EU Risk Management Plan
For Avtozma

(CT-P47, tocilizumab biosimilar)

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Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

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List of Abbreviations

Term	Explanation
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AI	Autoinjector
ALT	Alanine aminotransferase
ANC	Absolute neutrophil counts
AST	Aspartate aminotransferase
CHO	Chinese hamster ovary
CRS	Cytokine release syndrome
COVID-19	Coronavirus disease 2019
DMARDs	Disease-modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EMA	European medicines agency
EOS	End-of-study
GCA	Giant Cell Arteritis
GI	Gastrointestinal
GVP	Good pharmacovigilance practice
IgE	Immunoglobulin E
IL	Interleukin
ILD	Interstitial lung disease
IV	Intravenous
LDL	Low-density lipoprotein
PIL	Patient information leaflet
MTX	Methotrexate
NE	Not estimated
NMSC	Non-melanoma skin cancer
NSAID	Nonsteroidal anti-inflammatory drug
PFS	Pre-filled syringe
pJIA	Polyarticular juvenile idiopathic polyarthritis
PSUR	Periodic safety update report

Term	Explanation
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RMP	Risk management plan
sJIA	Systemic juvenile idiopathic arthritis
SC	Subcutaneous
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
TB	Tuberculosis
TC	Total cholesterol
TCZ	Tocilizumab
TEAE	Treatment Emergent Adverse Event
TNF	Tumour necrosis factor
ULN	Upper limit of normal

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Tocilizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AC07
Marketing Authorisation Applicant	Celltrion Healthcare Hungary Kft.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Avtozma
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	**Chemical class** Immunosuppressants, Interleukin inhibitors.
	Summary of mode of action Tocilizumab binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes, and fibroblasts. IL-6 is involved in diverse physiologic processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute-phase protein synthesis, and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia
	Important information about its composition: Tocilizumab, a humanised IgG1 monoclonal antibody against the human IL-6 receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology
Hyperlink to the Product Information	Product Information (Section 1.3.1)
Indication(s) in the EEA	**Current:** **Intravenous (IV) Formulation:** Avtozma (tocilizumab [TCZ]), in combination with methotrexate (MTX), is indicated for:

	Rheumatoid arthritis (RA) Treatment of severe, active, and progressive rheumatoid arthritis (RA) in adults not previously treated with MTX. The treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Systemic juvenile idiopathic arthritis (sJIA) 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. Avtozma can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Polyarticular juvenile idiopathic polyarthritis (pJIA) Avtozma in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic polyarthritis (pJIA; rheumatoid factor [RF] positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Cytokine release syndrome (CRS) Treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older. Coronavirus disease 2019 (COVID-19) Treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. **Subcutaneous (SC) Formulation:** Avtozma in combination with MTX, is indicated for: Rheumatoid arthritis (RA) Treatment of severe, active, and progressive RA in adults not

	previously treated with MTX. The treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or TNF antagonists. In these patients, Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Giant Cell arteritis (GCA) Treatment of Giant Cell Arteritis (GCA) in adult patients. Polyarticular juvenile idiopathic polyarthritis (pJIA) Treatment of juvenile idiopathic polyarthritis (pJIA; RF positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Avtozma can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Systemic juvenile idiopathic arthritis (sJIA) Treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Avtozma can be given alone (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
	Proposed: Not applicable
Dosage in the EEA	**Current:** **IV formulation:** RA Patients The recommended posology is 8 mg/kg body weight, given once every 4 weeks. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. sJIA Patients The recommended posology in patients above 2 years of age is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

	pJIA Patients The recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. CRS Patients (adults and paediatrics) The recommended posology for treatment of CRS given as a 60-minute intravenous infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. Avtozma can be given alone or in combination with corticosteroids. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to three additional doses of Avtozma may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients. COVID-19 Patients The recommended posology for treatment of adult patients with COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg, with a maximum dose of 800 mg. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of Avtozma 8 mg/kg may be administered. There should be an interval of at least 8 hours between these two infusions. **SC formulation:** RA: The recommended posology is subcutaneous 162 mg once every week. GCA: The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. Avtozma can be used alone following discontinuation of glucocorticoids. Avtozma monotherapy should not be used for the treatment of acute relapses. Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

	pJIA: The recommended posology in patients above 2 years of age is subcutaneous 162 mg once every 2 weeks in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 3 weeks in patients weighing less than 30 kg. sJIA: The recommended posology in patients above 1 year of age is subcutaneous 162 mg once every week in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 2 weeks in patients weighing less than 30 kg. Patients between 1 year and 2 years of age must have a minimum body weight of 10 kg when receiving Avtozma subcutaneously.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** **IV formulation:** *Concentrate for Solution for Infusion* Each milliliter (mL) concentrate contains 20 mg tocilizumab. • Each vial contains 80 mg of tocilizumab in 4 mL • Each vial contains 200 mg of tocilizumab in 10 mL • Each vial contains 400 mg of tocilizumab in 20 mL **SC formulation:** *Solution for Injection* Each pre-filled syringe (or pen) contains 162 mg of tocilizumab in 0.9 mL. • 162 mg/0.9 mL solution for injection in pre-filled syringe • 162 mg/0.9 mL solution for injection in pre-filled pen
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Avtozma, biosimilar tocilizumab and CT-P47 may be used in this document to describe the investigational product to which this application refers.

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

According to the Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

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

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

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
Repeat-dose toxicity of CT-P47 There were no test article related effects on mortality, clinical observations, body weight change, food consumption, ophthalmic examination, ECG parameters, haematology, macroscopic or microscopic observations. Findings observed during study included a decrease in fibrinogen levels, a decrease in globulin, an increase in albumin/globulin ratio (A/G ratio), a decrease in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine kinase, a decrease in urine volume, and differences in organ weight (kidney, pituitary, spleen and uterine). These findings, however, were not considered toxicologically relevant. In organ weight, decreased kidney weights relative to terminal body weight were observed in males treated with CT-P47 and EU-RoActemra. Decreased spleen weight (absolute and relative to body and brain weight) in males, increased pituitary weight relative to body weight in females and increased uterine weight relative to body weight in females were observed in group treated with EU-RoActemra, compared to the group treated with CT-P47. As there were no macroscopic or microscopic findings that could be attributed to the treatment with CT-P47 or EU-RoActemra, the differences between CT-P47 and EU-RoActemra detected in the organ weight were deemed to be incidental and it was considered that there was no toxicological concern. The administration of CT-P47 and EU-RoActemra subcutaneously once a week for 4 weeks at 100 mg/kg did not induce toxicologically relevant findings. There were no differences between CT-P47 and EU-RoActemra, except the increase in ALT, AST and creatine kinase in one female treated with CT-P47. Nevertheless, as no alterations were observed in organs, these increases are not considered toxicologically relevant. However, it should be mentioned that alterations in parameters such as ALT and AST are described in treatment with Actemra, the reference item, a marketed product (RoActemra SmPC). **Repeat-dose toxicity of RoActemra (European Public Assessment Report [EPAR])** Toxicity studies have shown tocilizumab to be well tolerated in cynomolgus monkeys, both as single intravenous (IV) doses up to 100 mg/kg and when given in multiple IV doses up to 50 mg/kg/day	Transient or intermittent mild and moderate elevations of hepatic transaminases may be observed by tocilizumab treatment.

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
for 4 weeks or at IV doses up to 100 mg/kg/week for 6 months. No major abnormal findings were observed in either the clinical pathology investigations or in the histopathological evaluation of tissues. The systemic steady state exposure to tocilizumab in these monkey studies was 8-to10-fold above the maximum human exposure comparing trough levels in the animals with the maximum level measured in clinical trials. Changes in haematological parameters were observed, e.g. decrease in red blood cell count or increased lymphocyte count. A signal toward reduction of neutrophils was observed in the 2-week toxicity study with a clear pronounced manifestation in the 4-week daily treatment cynomolgus study with no manifestation in the bone marrow. The absence of bone marrow myeloid hyper or hypoplasia in the presence of reduced absolute neutrophil counts (ANCs) along with the lack of neutrophil morphological abnormalities strongly suggests that neither peripheral sequestration nor incomplete granulopoiesis is the underlying mechanism of the reduced circulating neutrophils. The studies demonstrated that inhibition of IL-6 normalizes the inflammation-driven osteoclastic bone destruction and safety studies conducted with tocilizumab demonstrated that a morphologically and functionally normal bone homeostasis is maintained under continuous chronic IL-6 inhibition with tocilizumab.	
Reproductive/Developmental toxicity of CT-P47 Reproductive toxicology studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Reproductive/Developmental toxicity of RoActemra (RMP)** Tocilizumab was not teratogenic in an embryo-foetal toxicity study (Study TOX00-0012) in cynomolgus monkey at a daily dose of 50 mg/kg/day (highest dose) associated with a high systemic cumulative exposure of > 100 above the expected human efficacious concentration. A higher rate of abortion was however noted in this dose group compared with the placebo and other low dose groups. The abortion incidence was within the historical background for the cynomolgus monkey in captivity (Boot et al.	Although IL-6 does not seem to be a critical cytokine for either foetal growth or the immunological control of the maternal/foetal interface, the relevance of this observation for human pregnancy is unknown. However, a possible relation to tocilizumab cannot be excluded as preclinical data suggest an increased risk of spontaneous abortion. Therefore, tocilizumab may

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
1985; Vogel and Bee 1999; Hendrie et. al. 1996) and the individual cases of abortions/embryo-foetal death did not show any consistent relationship to dosing or duration of dosing with tocilizumab. IL-6 does not appear to be a critical cytokine for embryo-foetal development since IL-6 deficient mice are fertile and their offspring show no abnormal phenotype. In addition, the abortion rate in the cynomolgus monkey study was only marginally higher in the high dose group compared to the other treatment groups. Transfer of a murine analog of tocilizumab into the milk of lactating mice has been observed (Report 1003—Mogi M. RO4877533). Preclinical data in mice do not suggest an effect on fertility in mice treated with a mouse IL-6R surrogate antibody for tocilizumab (Report 1033493 – Arima A. RO4877533; Report 1033494 – Arima A. RO4877533). With this antibody, there was also no evidence for IL-6-inhibition-related effects on pre-natal and postnatal development, including on developing immune function in the F1 generation treated transplacentally (Report 1003492 – Arima A. RO4877533). Similarly, there were no toxicologically relevant effects noted on fertility, pre- and postnatal development, and immune function in a combined fertility and pre- and postnatal development study in IL-6 knockout mice (Report 1029892 – Hoberman A).	represent a potential risk to pregnancy. No teratogenic effects have been identified with tocilizumab.
Genotoxicity/carcinogenicity of CT-P47 Genotoxicity/carcinogenicity studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Genotoxicity/carcinogenicity of RoActemra (RMP)** A carcinogenicity study of tocilizumab has not been conducted. As tocilizumab does not bind to rodent IL-6R, conventional long-term carcinogenicity studies in rats or mice are thus, inappropriate to assess a function-associated carcinogenic potential of tocilizumab. A standard test set of in vitro genotoxicity studies conducted with tocilizumab has shown no evidence of genotoxic liabilities (Study TOX02-0172-JITSU97-0035; Study TOX02-0171-JITSU97-0086). IgG macromolecules do not penetrate cell walls or cell membranes and therefore, do not have direct interactions with cellular DNA. Because of this, IgG1 monoclonal antibodies do not	The risk of malignancy is known to be increased in patients with RA, compared with the general population, and with some treatments commonly used in RA, such as MTX and biologic DMARDs (Bongartz et al. 2006). A Food and Drug Administration (FDA) alert was published requiring manufacturers of TNF blockers to update the Boxed Warning in the prescribing information to alert

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
have an intrinsic carcinogenic potential, and thus, such tests are not considered to be of relevance for a carcinogenic risk assessment of antibodies. IL-6 is recognized as one of the most potent autocrine growth factors in the pathogenesis of numerous cancers, including thyroid carcinomas (Russell et al. 2004), prostate and ovarian cancer (Xiao et al. 2004; Hefler et al. 2003) and, in particular, hematologic malignancies such as multiple myeloma (Hilbert et al. 1995; Siegall et al.1990). Recently published data further demonstrated the contributing role of the sIL-6R transignalling in a colon cancer model (Becker et al. 2004; Becker et al. 2005; Landi et al. 2003), suggesting that under conditions of chronic inflammation, IL-6 may contribute to malignant progression and resistance of various malignancies (through activation of gp130), which do not per se express the membrane-bound IL-6 receptor. While the direct stimulatory activity of IL-6 has long been recognized, recent studies have identified and characterized the role of IL-6 in the regulation of the signal transducer and activator of transcription 3 (STAT3), its critical role in tumour progression, and the negative interference of STAT3-regulated gene products in tumour immunosurveillance (Yu 2007). Not only does STAT3, constitutively activated by malignant cells, inhibit the expression of mediators necessary for effective immune activation against tumour cells, but it also actively promotes the production of immunosuppressive factors that lead to a blockade of efficient anti-tumour response in situ. Recently published data demonstrated that the functional maturation of dendritic cells in the tumor environment, which is necessary for an effective activation of an anti-tumour response, is blocked by tumour-secreted IL-6 (Park et al. 2004), an effect which significantly contributes to the widely observed clinical phenomenon of tumour tolerance rather than rejection. Conversely, the potential role of IL-6 as a therapeutic anti-tumour agent has been shown in a variety of preclinical tumour models although the use of recombinant IL-6 in patients was determined to be a multiple myeloma inducing growth factor (Mullen et al. 1992; Sun et al. 1992; Abroun et al. 2004; Salazar-Onfray et al. 2007). Consistent with the role of IL-6 in tumour progression, nonclinical pharmacology studies conducted with tocilizumab showed clear anti-proliferative effects. These experiments demonstrated that tocilizumab inhibits the proliferation of cell lines induced by IL-6/sIL-6R complex such as BAF-h130 (Study PHM02-0148) and	healthcare professionals of an increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers. EMA 2010 priorities also identified the risk of malignancy as one of the potential long-term adverse effects of immunomodulators, including the anti-TNFs, rituximab, and tocilizumab. Malignancies are considered an important potential risk associated with TCZ use.

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
effectively stops the IL-6 dependent growth of human myeloma cell lines in vitro (Study PHM02-0249) and KPMM2 tumour cells in vivo (Study PHM04-0089 [J97-0262]). The therapeutic effect of IL-6 receptor blockage under in vivo conditions was shown in various disease models with MR16-1, a rodent-specific analog antibody to tocilizumab. MR16-1 completely prevented the lymphoproliferative manifestations in an IL-6 transgenic mouse model of Castleman's Disease (Katsume et al. 2002) and halted the progression of tumour growth in a mouse model of colon carcinoma (Becker et al. 2004). No lesions with a proliferative characteristic or any other type of pre-neoplastic findings have been seen in a cynomolgus monkey study of 6-months, in which the animals were continuously exposed to tocilizumab at serum concentrations more than 30-fold above the clinical effective serum levels. As suggested by the role of IL-6 in the physiology of cell regulation, chronic and complete IL-6 depletion in vivo in IL-6 knockout mice does not lead to a higher spontaneous malignancy rate. Reports from experiments conducted in aged IL-6 knockout mice are particularly notable, as the life span was not compromised nor was there any palpable mass reported in these animals (Gomez et al. 2006; Dovi et al. 2003), although tissues of these animals were not histopathologically screened for the presence of early stage malignant disease. There is no direct evidence that tocilizumab would induce malignant transformation. On the contrary, other available evidence that IL-6 is a growth factor for tissue maintenance and regeneration under conditions of insult (direct damage or inflammation), and in malignant cells, IL-6 per se does not seem to disrupt the balance of the immunological control of tumour growth and metastasis (immunosurveillance). The nonclinical data suggest an association between elevated levels of IL-6 and tissue/tumour growth, but do not suggest that an inhibition of the IL-6R signalling pathways via chronic treatment with tocilizumab would lead to an increased risk of malignancies in patients.	
General Safety Pharmacology of CT-P47 No specific safety pharmacology studies were performed. Safety end-points were incorporated into the monkey repeat-dose toxicity study. No CT-P47- or RoActemra-related clinical observations and changes to ECG parameters were noted. This approach is compatible with the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/	Tocilizumab has not demonstrated an impact on cardiac integrity or electrophysiology in the clinical setting. Cardiovascular concerns are an

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **General Safety Pharmacology of RoActemra (RMP)** The cardiovascular safety of tocilizumab has been investigated in a series of rigorously designed preclinical in vivo studies. These results indicate that tocilizumab does not adversely affect either cardiac integrity or electrophysiology; an alteration of blood pressure was also not observed in any of the preclinical studies (Study TOX02-0127; Study TOX02-0158).	important potential risk because TCZ treatment is associated with increases in LDL cholesterol and triglycerides, and RA patients are at increased risk of cardiovascular disease.
Mechanisms for Drug Interactions of CT-P47 Drug Interactions studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Mechanisms for Drug Interactions of RoActemra (EPAR)** Pharmacodynamic drug interaction studies were not conducted with tocilizumab.	Not applicable
Juvenile Toxicity Studies of CT-P47 Juvenile toxicity studies have not been performed because they are not required according to the EMA guidance on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/ 42832/2005 Rev1) and EMA guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). **Juvenile Toxicity Studies of RoActemra (RMP)** Effects of a blockage of IL-6 signaling in juvenile animals have been investigated with a murine surrogate antibody of tocilizumab, termed MR16-1. MR16-1, a rat anti-mouse IL-6R monoclonal antibody (IgG1) has been thoroughly characterized in pharmacologic models as a suitable rodent analog of human anti-IL-6 antibodies. For this safety assessment purpose, juvenile mice were treated once every 3 days from weaning (postnatal Day 22) until sexual maturation (postnatal Day 79). Effects of MR16-1	None

Key Safety findings (from non-clinical studies) of CT-P47 (RoActemra biosimilar)	Relevance to human usage
were investigated on postnatal development and growth, immune system, skeletal development, and sexual maturation after IV administration of MR16-1 in juvenile mice. Toxicokinetic investigations yielded evidence that the study was done under full blockage of IL-6 signalling. The observation of anti-drug antibodies did not impair the assessment. No adverse effects were observed in body weight, food consumption, haematology, necropsy, organ weights, or histopathology in any treatment group during dosing or recovery period. With respect to immune system in juvenile animals, there were no adverse effects in immunocompetence, NK cell activities in any treatment group. The following results were obtained: 50- and 15-mg/kg groups, a decrease in CD3e+CD4+CD8a− ratio and peripheral blood count in males and females at end of the dosing period; decrease in CD3e+ ratio and count; increase in CD3e+CD4+CD8a− ratio and peripheral blood count in males and females and increase in CD49b/Pan-NK cells+CD3e− ratio in females in the 50-mg/kg group at end of the recovery period, was observed. These changes are considered to have a minor impact on the immune system, since no adverse effects on immunocompetence (serum IgG and IgM production to KLH) was observed in any treatment group. With respect to sexual maturation and skeletal development in juvenile animals, there were no adverse effects in the morphological differentiation of external genitalia, estrous cycle, sperm examination, crown-rump length, or skeletal development in any treatment group. From these study results, it is concluded that MR16-1 did not induce any toxicologically meaningful changes on postnatal development, growth, immune system, skeletal development, or sexual maturation in juvenile animals.	

Conclusion on Non-Clinical Data

Non-clinical investigations comparing CT-P47 with the reference product have not shown them to behave differently from one another in any relevant respects. No unexpected safety findings or signals were identified in the non-clinical programme for CT-P47.

Part II: Module SIII - Clinical trial exposure

The clinical development programme for Avtozma (CT-P47) includes three completed Phase 1 clinical studies in healthy subjects (Studies CT-P47 1.1, 1.2 and 1.3) and two completed Phase 3 studies in patients with moderate to severe active rheumatoid arthritis (Studies CT-P47 3.1 and 3.2).

- **Study CT-P47 1.1**: a Phase 1, randomised, double-blind, two-arm, parallel group, single-dose study to compare pharmacokinetics and safety of two subcutaneous injection formulations of tocilizumab (CT-P47 and EU-approved RoActemra) in 313 healthy subjects. Of those, 158 and 155 subjects received CT-P47, and EU-approved RoActemra, respectively.

- **Study CT-P47 1.2**: a Phase 1, randomized, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of three intravenous infusion formulations of tocilizumab (CT-P47, EU-approved RoActemra, US-licensed Actemra) in 132 healthy Japanese subjects. Of those, 45, 43 and 44 subjects received CT-P47, EU-approved RoActemra and US-licensed Actemra, respectively.

- **Study CT-P47 1.3:** a Phase 1, randomized, open-label, two-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of the auto-injector and pre-filled syringe of CT-P47 in 310 healthy subjects. Of those, 153 and 157 subjects received CT-P47 AI and CT-P47 PFS, respectively.

- **Study CT-P47 3.1** (pivotal study): a randomized, active-controlled, double-blind, phase 3 study to compare efficacy and safety of two intravenous infusion formulations of tocilizumab (CT-P47 and RoActemra) when co-administered with methotrexate in patients with moderate to severe active rheumatoid arthritis. This study consisted of 471 patients with moderate to severe active RA, aged between 18 and 75 years, randomly assigned to receive 8 mg/kg of CT-P47 or RoActemra administered by IV every 4 weeks (Q4W) in combination with MTX (between 10 to 25 mg/week, oral or parenteral; intramuscular or subcutaneous dose) and folic acid (≥5 mg/week, oral dose). The MTX dose and route planned to be maintained from the beginning to the end-of-study (EOS). This study included a Screening Period, Treatment Period (I and II), and End-of-Study (EOS) visit. The maximum duration of the study per patient was 58 weeks: a Screening Period of 6 weeks, Treatment Period I of 24 weeks, Treatment Period II of 24 weeks, and EOS visit of 4weeks. The patients received CT-P47 or RoActemra up to Week 20. Patients in the RoActemra treatment group underwent randomization process in a ratio of 1:1 to either continue with RoActemra or to transition to CT-P47 prior to study drug administration at Week 24. The EOS visit was performed at Week 52 including assessment of efficacy and safety.

- **Study CT-P47 3.2**: a single-arm, open-label, multiple-dose, phase 3 study to evaluate usability of the subcutaneous auto-injector (AI) for CT-P47 in patients with moderate to severe active rheumatoid arthritis. This study consisted of 33 patients with moderate to severe active RA, aged between 18 and 70 years, assigned to receive 162 mg of CT-P47 AI then CT-P47 pre-filled syringe (PFS). All patients also received the combination of MTX (between 10 to 25 mg/week, oral or parenteral dose) and folic acid (≥5 mg/week, oral dose) along with the study drug. The MTX dose and route were maintained from the beginning to the end-of-study (EOS). This study included a Screening period, Treatment period, and End-of-Study (EOS)visit/Early

withdrawal (EW) visit. The maximum duration of the study per patient was 18 weeks: a Screening Period of 6 weeks, and a Treatment Period of 12 weeks including EOS visit.

The patient exposure from the studies CT-P47 3.1 and 3.2 are presented in the following tables.

Participants in studies CT-P47 1.1, 1.2 and 1.3 have not been included in the tables below because these studies were conducted in healthy subjects (as opposed to patients), who were exposed to single doses.

Table 3: Exposure by duration

INDICATION: Rheumatoid Arthritis										
	CT-P47								Tocilizumab IV reference product** (N=237)	
	Total (N=377)		CT-P47 IV (N=234)		CT-P47 SC (N=33)		Switched from Tocilizumab IV reference product* (N=110)			
Duration of exposure [1,2]	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Duration < 4 weeks	9	63	1	1	4	58	4	4	1	26
4 weeks ≤ Duration < 10 weeks	6	360	2	87	3	207	1	66	7	271
10 weeks ≤ Duration < 24 weeks	51	5370	6	674	26	1868	19	2828	31	4714
24 weeks ≤ Duration < 48 weeks	119	24090	33	9403	0	0	86	14687	108	20625
48 weeks ≤ Duration	192	65446	192	65446	0	0	0	0	90	30538
Total	377	95329	234	75611	33	2133	110	17585	237	56174

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** Exposure to reference product during Treatment Period 1 in the switching arm is included in this column.
Person time (days) = ([Date of Last Exposure to Treatment] - [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1).
[1] The longest duration of exposure is 52.1 weeks.
[2] Duration of exposure (weeks) = (Person time in days) /7.
Abbreviation: IV = Intravenous; SC = Subcutaneous
Protocol Number: CT-P47 3.1, CT-P47 3.2

Table 4: Exposure by number of treatments received

INDICATION: Rheumatoid Arthritis										
	CT-P47								Tocilizumab IV reference product** (N=237)	
	Total (N=377)		CT-P47 IV (N=234)		CT-P47 SC (N=33)		Switched from Tocilizumab IV reference product* (N=110)			
Number of treatment administration	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)
1	6	6	1	1	1	1	4	4	0	0
2	3	59	1	29	2	30	0	0	6	171
3	5	419	1	58	1	27	3	334	2	126
4	8	1055	5	604	0	0	3	451	5	622
5	2	199	0	0	1	71	1	128	14	2273
6	39	4508	3	495	20	1426	16	2587	102	17310
7	87	14771	4	690	0	0	83	14081	3	548
8	2	146	0	0	2	146	0	0	0	0
9	10	1419	4	987	6	432	0	0	3	681
10	6	1810	6	1810	0	0	0	0	1	337
11	13	4238	13	4238	0	0	0	0	7	2354
12	30	10188	30	10188	0	0	0	0	18	5988
13	166	56511	166	56511	0	0	0	0	76	25764
Total	377	95329	234	75611	33	2133	110	17585	237	56174
Total Cumulative Dose (mg)										
Mean	5413.6		6899.1		996.5		3578.5		4892.3	
Median	5434.0		6957.5		972.0		3691.0		4313.0	
Minimum	162		744		162		244		776	

INDICATION: Rheumatoid Arthritis										
	CT-P47								Tocilizumab IV reference product** (N=237)	
	Total (N=377)		CT-P47 IV (N=234)		CT-P47 SC (N=33)		Switched from Tocilizumab IV reference product* (N=110)			
Number of treatment administration	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Maximum	10400		10400		1458		5600		10400	

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** Exposure to reference product during Treatment Period 1 in the switching arm is included in this column.
Person time (days) = ([Date of Last Exposure to Treatment] - [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1).
Abbreviation: IV = Intravenous; SC = Subcutaneous
Protocol Number: CT-P47 3.1, CT-P47 3.2

Table 5: Exposure by age and gender

INDICATION: Rheumatoid Arthritis																				
Age group (years)	CT-P47																Tocilizumab IV reference product** (N=237)			
	Total (N=377)				CT-P47 IV (N=234)				CT-P47 SC (N=33)				Switched from Tocilizumab IV reference product* (N=110)							
	Patients (n)		Person time (days)		Patients (n)		Person time (days)		Patients (n)		Person time (days)		Patients (n)		Person time (days)		Patients (n)		Person time (days)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
18 - 64	66	234	16362	58236	41	139	12975	45346	8	22	580	1340	17	73	2807	11550	44	141	11562	31358
65 - 70	15	48	4086	12785	10	35	3380	10917	1	2	71	142	4	11	635	1726	10	29	2605	7456
71 - 75	2	12	595	3265	2	7	595	2398	0	0	0	0	0	5	0	867	3	10	978	2215
> 75	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	83	294	21043	74286	53	181	16950	58661	9	24	651	1482	21	89	3442	14143	57	180	15145	41029

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** Exposure to reference product during Treatment Period 1 in the switching arm is included in this column.
Person time (days) = ([Date of Last Exposure to Treatment] - [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1).
Abbreviation: IV = Intravenous; SC = Subcutaneous
Protocol Number: CT-P47 3.1, CT-P47 3.2

Table 6: Exposure by Racial Group

INDICATION: Rheumatoid Arthritis										
	CT-P47								Tocilizumab IV reference product ** (N=237)	
	Total (N=377)		CT-P47 IV (N=234)		CT-P47 SC (N=33)		Switched from Tocilizumab IV reference product * (N=110)			
Race	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)	Patients (n)	Person time (days)
White	377	95329	234	75611	33	2133	110	17585	237	56174
Other	0	0	0	0	0	0	0	0	0	0
Total	377	95329	234	75611	33	2133	110	17585	237	56174

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** Exposure to reference product during Treatment Period 1 in the switching arm is included in this column.
Person time (days) = ([Date of Last Exposure to Treatment] - [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] - [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch - 1] - [Date of First Exposure to Treatment] + 1).
Abbreviation: IV = Intravenous; SC = Subcutaneous
Protocol Number: CT-P47 3.1, CT-P47 3.2

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

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

The important exclusion criteria from the clinical studies, CT-P47 3.1 and 3.2, are presented below.

Patient who has previously received investigational or licensed product; targeted synthetic DMARD(s) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or an IL-6 inhibitor for any purposes. Patient who has previously received more than 1 biologic agents approved for the treatment of RA

Patient who has received or plans to receive any of the following prohibited medications or treatment: Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1), Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1), Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer, Alkylating agents within 1 year prior to the first administration of the study drug (Day 1), Herbal treatment within 2 weeks prior to the first administration of the study drug (Day 1), Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 1), or any planned live or live-attenuated vaccination during the study period, Any surgical procedure, including bone or joint surgery or synovectomy

Reason for exclusion: The above-mentioned exclusion criteria were applied to prevent misinterpreting observations about study-related treatment that were actually due to prior therapies.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned criteria were excluded to prevent interference with efficacy and safety study endpoints.

Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products

Reason for exclusion: Patients with hypersensitivity to monoclonal antibodies when treated with tocilizumab were excluded from the clinical development programme for safety reasons. Patients with a known hypersensitivity would be at risk of serious systemic hypersensitivity reactions.

Is it considered to be included as missing information?: No

Rationale: The use of tocilizumab is contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients. This is adequately described in the Summary of product characteristics (SmPC) of Avtozma (Section 4.3 ‘Contraindications’).

Patient who currently has, or has a history of, a known infection with hepatitis B (active or carrier of hepatitis B) or hepatitis C, or infection with human immunodeficiency virus (HIV), acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1), recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1), past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as

histoplasmosis), Other serious infections within 24 weeks prior to the first administration of the study drug (Day 1)

Reason for exclusion: Patients with history of chronic or recurrent infections and active infections may be at an increased risk of infections when treated with tocilizumab. Hence, the patients with above mentioned conditions were excluded from the clinical programme to prevent interference with safety study endpoints.

Is it considered to be included as missing information?: No

Rationale: Serious infection is an important identified risk of tocilizumab for chronic tocilizumab dosing, and the use of tocilizumab is contraindicated in patients with active severe infections. This is adequately described in the SmPC of Avtozma (Section 4.3 'Contraindications' and Section 4.4. 'Special warnings and precautions for use'), which includes the precautions to be taken while using tocilizumab.

Patient who currently has, or has a history of, any of the following tuberculosis (TB): Patient who has current or a history of active TB, Patient who has signs or symptoms suggestive of active TB, Patient who has had exposure to a person with active TB such as first-degree family members or co-workers within 16 weeks prior to the first administration of the study drug (Day 1), Patient who has a past diagnosis of latent TB unless they have documentation of completing TB prophylaxis, Patient who has a current diagnosis of latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest X-ray), Patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening

Reason for exclusion: Patients with above mentioned conditions were excluded from the clinical study to prevent interference with safety study endpoints.

Is it considered to be included as missing information?: No

Rationale: The use of tocilizumab is contraindicated in patients with active severe infections. The precautions to be taken for the management of tuberculosis before starting treatment or during treatment with Avtozma is adequately described in the SmPC (Section 4.4 'Special warnings and precautions for use' and Section 4.8 'Undesirable effects').

Patient who has a medical condition including one or more of the following: Current uncontrolled diabetes mellitus, even after insulin treatment, Current uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg), Any other current inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or fibromyalgia, Current significant systemic RA involvement (e.g., Sjögren's syndrome, vasculitis, pulmonary fibrosis), History of organ transplantation, current respiratory disease, Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome, current or history of serious acute or chronic medical or psychiatric condition, any other clinically significant disorder, condition, or disease

Reason for exclusion: Patients with above mentioned conditions were excluded from the clinical study to prevent interference with safety study endpoints and to ensure patient safety.

Is it considered to be included as missing information?: No

Rationale: Demyelinating disorders is an important potential risk for Avtozma. There is no evidence to suggest that tocilizumab may have an effect on pulmonary, renal, or endocrine function or demyelinating disorders including multiple sclerosis and Guillain-Barre syndrome.

Current or history of diverticulitis, chronic ulcerative lower gastrointestinal tract disease or any other gastrointestinal condition that may predispose to perforation

Reason for exclusion: Patients with above mentioned conditions were excluded from the clinical study to prevent interference with safety study endpoints and to ensure patient safety.

Is it considered to be included as missing information?: No

Rationale: Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with tocilizumab in RA patients. Complications of diverticulitis is an important identified risk of tocilizumab for chronic tocilizumab dosing, and this is adequately described in the SmPC of Avtozma (Section 4.4 'Special warnings and precautions for use' and Section 4.8 'Undesirable effects').

A known malignancy within the previous 5 years prior to the first administration of the study drug

Reason for exclusion: This population was excluded from the clinical programme to ensure the safety of the patients to be treated with tocilizumab. Moreover, the patients with history of past or concurrent malignancy are prone to frequent hospitalisation, hence higher dropout rates.

Is it considered to be included as missing information?: No

Rationale: 'Malignancies' is an important potential risk for tocilizumab. The risk of malignancy is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancy. The increased risk of malignancy is adequately described in the SmPC of Avtozma (Section 4.4 'Special warnings and precautions for use').

Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed within 6 months of the last dose of study drug. Male patient who is planning to donate sperm or father a child within 6 months of the last dose of study drug.

Reason for exclusion: Female patients who are pregnant or breastfeeding were excluded from the clinical development programme for safety reasons, to minimise risk to pregnant women and nursing mothers and their children.

Is it considered to be included as missing information?: No

Rationale: Based on non-clinical studies there is an increased risk of spontaneous abortion/embryo-foetal death at a high dose.

This is adequately described in the SmPC of Avtozma (Section 4.6 'Fertility, pregnancy and lactation') which states that tocilizumab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus and women of childbearing potential should use effective contraception during treatment and for up to 3 months after treatment with tocilizumab.

Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 1 years from Screening.

Reason for exclusion: This population has been excluded as a technical requirement. The patients with ongoing and past abuse history have a potential for non-adherence to study protocol.

Is it considered to be included as missing information?: No

Rationale: The exclusion of this population is not related to the safety of the patient population and it is not a safety concern for the reference product, RoActemra. These conditions may have a confounding impact on the efficacy assessment.

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, or adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

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

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

Type of special population	Exposure
Paediatric patients	Children less than 18 years of age were not included in the clinical development programme of CT-P47 (see Table 5).
Elderly patients	Overall, 17 (4.5%) male and 60 (16.0%) female patients aged ≥ 65 years received CT-P47 in the study CT-P47 3.1 and 3.2 (see Table 5).
Pregnant or Breastfeeding women	Pregnant or breastfeeding women were not included in the clinical development programme of CT-P47.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with hepatic impairment were not studied in the clinical development programme. None of the patients entered into studies of CT-P47 had evidence of hepatic impairment.
Patients with renal impairment	Patients with renal impairment were not studied in the clinical development programme. None of the patients entered into studies of CT-P47 had evidence of renal impairment.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not studied in the clinical development programme of CT-P47.
Population with relevant different ethnic origin	All patients in the clinical trial programme who received CT-P47 were of Caucasian (White) origin (377 patients) (see Table 6). Ethnic origin is not known to be relevant to the response to treatment with tocilizumab.
Immunocompromised patients	Not included in the clinical development programme of CT-P47.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme of CT-P47.

Type of special population	Exposure
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as the product has not received marketing authorisation yet in any jurisdiction.

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

Based on the given mechanism of action of the tocilizumab and its indications, the potential for misuse or abuse for illegal purposes is considered negligible.

Part II: Module SVII - Identified and potential risks

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

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

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

1. Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

None.

2. 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:

None.

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

In accordance with the EU requirement, Avtozma has been shown to have quality, safety and efficacy comparable to the reference product RoActemra. The safety profile of Avtozma has been adequately described in the product information.

The following risks are labelled in the product information for the reference product and are not important safety concerns for either Avtozma or RoActemra:

Upper respiratory tract infections, Cellulitis, Hypothyroidism, Pneumonia, Oral herpes simplex, Herpes zoster, Leukopenia, Hypofibrinogenaemia, Anaphylaxis (fatal), Headache, Dizziness, Conjunctivitis, Hypertension, Cough, Dyspnoea, Abdominal pain, Mouth ulceration, Gastritis, Stomatitis, Gastric ulcer, Rash, Pruritus, Urticaria, Stevens-Johnson-Syndrome, Nephrolithiasis, Peripheral oedema, Hypersensitivity reactions, and Weight increased.

4. Known risks that do not impact the risk-benefit profile:

None.

5. Other reasons for considering the risks not important:

None.

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

Important identified risk: Serious infections

Risk-benefit impact:

Serious infection is an important identified risk of Avtozma as the patients with RA, GCA, pJIA, sJIA are at an increased risk of developing infections. Serious infection is an important potential risk for treatment of COVID-19 as the risk has yet to be confirmed in this population.

Biologic disease-modifying anti-rheumatic drugs (DMARDs) have dramatically improved the management of rheumatoid arthritis (RA) as they are highly effective in reducing systemic inflammation and RA disease activity via inhibition of the cytokine pathways or T-cell or B-cell functions. Biologic DMARDs are, however, associated with an increased risk of serious infections due to their immunosuppressive effect (Jeon et al., 2021)

Due to a combination of virus- and drug-induced immunosuppression, critically ill patients with COVID-19 may even have a higher risk of developing a secondary infection. These secondary infections can aggravate the severity of illness and increase the risk of death (De Bruyn et al., 2022).

According to the SmPC of the reference product RoActemra, in the long-term exposure population of RoActemra clinical studies, the overall rate of serious infections (bacterial, viral and fungal) was 4.7 events per 100 Patient Years (PY). In 6-month controlled clinical studies, the rate of serious infections with RoActemra 8 mg/kg plus DMARDs was 5.3 events per 100 PYs.

The use of Avtozma is contraindicated in the patients with active, severe infections. Caution must be exercised before initiating treatment in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes, and interstitial lung disease [ILD]) which may predispose patients to infections. The patients should be regularly monitored for timely identification of serious infections. COVID-19 patients should immediately seek medical help if they identify any symptoms of infection.

The benefits of an effective treatment with Avtozma outweigh the risk of serious infection, which can be managed by following the guidance provided in the SmPC.

Important identified risk: Complications of Diverticulitis

Risk-benefit impact:

The safety concern “complications of diverticulitis” is an important identified risk for all indications for tocilizumab with one exception. “Complications of diverticulitis” is an important potential risk for tocilizumab when the indication for treatment is COVID-19.

Diverticulitis refers to the inflammation of diverticula, which are pouch-like protrusions in the walls of the colon. The symptoms may begin when compaction of faecal material abrades the weak walls of the diverticula and bacteria get trapped causing inflammation or sometimes microperforations.

The proportion of patients exposed to the reference product RoActemra, who experienced complications of diverticulitis in the clinical studies with RoActemra, ranged from 0 to 0.20 events per 100 PYs. (RoActemra RMP)

As per the SmPC of the reference product RoActemra and Avtozma, tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. 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.

As per the SmPC of the reference product RoActemra and Avtozma, complications of diverticulitis are reported with uncommon frequency.

The benefits of an effective treatment with Avtozma outweigh the risk of complications of diverticulitis which can be managed by following the guidance provided in the SmPC.

Important identified risk: Neutropenia

Risk-benefit impact:

Neutropenia is a condition characterised by neutrophil count below 1500/µL. Neutrophils play a role in the immune defence against extracellular bacteria, including *Staphylococci*, *Streptococci*, and *Escherichia coli,* among others. Low neutrophil count is associated with recurrent infections, and opportunistic infections.

In the clinical studies with RoActemra, the proportion of patients in RoActemra IV RA population, who developed Grade 4 neutropenia was less than 1%, while 5.4% experienced Grade 3 neutropenia. In the SC RA population, the proportion of patients who developed Grade 3 and Grade 4 neutropenia ranges from 3.5% to 5.6% depending on the posology for tocilizumab. No correlation was observed between events of Grade 3 and 4 neutropenia and the occurrence of serious infections.

In the COVID-19 population treated with the reference product, the proportion of patients who developed Grade 4 neutropenia ranged from 0% to 1.2% (WA42380, ML42528and WA42511 studies). 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.

This safety concern does not have an impact on the benefit-risk balance of Avtozma. The benefits of an effective treatment with Avtozma outweigh the risk of neutropenia which can be managed with the information provided in SmPC, Patient Information Leaflet, and Educational Materials for Healthcare professionals and patients.

Important identified risk: Hepatotoxicity

Risk-benefit impact:

Tocilizumab has been associated with Hepatotoxicity ranging from mild serum aminotransferase elevations to liver injury with jaundice and occasional reactivation of hepatitis B. Liver injury is commonly observed in patients infected with coronavirus.

In the clinical studies with the reference product RoActemra, in patients with moderate to severe RA and treated with tocilizumab, elevations in Alanine aminotransferase (ALT) or Aspartate Aminotransferase (AST) >3 x Upper limit of normal (ULN) occurred in 5.3% and 2.2% patients, respectively (Study WA25204). Three serious hepatic events occurred in the tocilizumab arm including 2 events of Hepatitis and 1 event of Hepatic Encephalopathy.

As per the SmPC of the reference product RoActemra and Avtozma, Drug-induced liver injury, is a rarely reported adverse event. The risk of hepatotoxicity is described in the SmPC and recommendation for monitoring of elevated transaminases is provided.

The benefits of an effective treatment with Avtozma outweigh the apparent risk of Hepatotoxicity, for which effective risk management strategies are available.

Important potential risk: Thrombocytopenia and the potential risk of bleeding

Risk-benefit impact:

Thrombocytopenia is a platelet count below the lower limit of normal, i.e., 150 x 10^3/µL (for adults) and the risks associated with it range from no risk at all to bleeding risks and thrombosis. The correlation of severity of thrombocytopenia and bleeding risk is uncertain (Jinna et al., 2023).

According to the SmPC of the reference product RoActemra and Avtozma, decreases in platelet counts have occurred following treatment with RoActemra. The platelets should be monitored according to good clinical practice.

In 6-month controlled trials conducted with the reference product, 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.

The benefits of an effective treatment with Avtozma outweigh the apparent risk of Thrombocytopenia and the Potential Risk of Bleeding, for which effective risk management strategies are available.

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

Risk-benefit impact:

Elevation in the blood levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides has been shown to be an independent predictor of many cardiovascular and cerebrovascular events (Alloubani et al., 2021).

In the clinical studies with RoActemra, increases in total cholesterol, LDL, and triglyceride levels have been observed in patients following treatment with tocilizumab. However, no association between elevated lipid levels and potential risk of cardiovascular and cerebrovascular events has been identified. (RoActemra RMP)

During routine laboratory monitoring with the reference product approximately 24% of patients receiving tocilizumab in clinical trials experienced sustained elevations in total cholesterol ≥6.2 mmol/L, with 15% experiencing a sustained increase in LDL to ≥4.1 mmol/L. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

As per the SmPC of the reference product RoActemra and Avtozma, Hypercholesterolaemia is a very common ADR and Hypertriglyceridaemia is an uncommon ADR associated with tocilizumab. An assessment of lipid parameters should be performed 4 to 8 weeks following initiation of tocilizumab therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

The benefits of an effective treatment with Avtozma outweigh the apparent risk of Elevated Lipid Levels and Potential Risk of Cardiovascular and Cerebrovascular Events for which effective risk management strategies are available.

Important potential risk: Malignancies

Risk-benefit impact:

The risk of malignancy is increased in patients with RA. A higher risk of cancer has consistently been reported in RA patients compared with the general population. Immunomodulatory medicinal products may increase the risk of malignancy.

In the RoActemra clinical development programme, there have been very few reports of cancer. Since the clinical data available for the reference product RoActemra are insufficient to assess the potential

incidence of malignancy following exposure to tocilizumab, malignancies are considered a potential risk. (RoActemra RMP)

As per the RMP of the reference product RoActemra, Tocilizumab treatment should not be started in subjects with cancer.

The available cumulative information does not provide evidence for an increased risk of malignancies in patients treated with tocilizumab. The benefits of an effective treatment with Avtozma outweigh the risk of malignancies.

Important potential risk: Demyelinating disorders

Risk-benefit impact:

Demyelination describes a loss of myelin sheath with relative preservation of axons. This results from diseases that damage myelin sheaths or the cells that form them. Demyelinating Disorders can be classified according to their pathogenesis into several categories: demyelination due to inflammatory processes, viral demyelination, demyelination caused by acquired metabolic derangements, hypoxic–ischaemic forms of demyelination and demyelination caused by focal compression (Love, 2006).

In the clinical development programme of the reference product RoActemra, there have been very few reports of nerve damage (demyelination) in patients treated with tocilizumab. Although the risk is unknown, the events are expected to be serious by nature. (RoActemra RMP)

As per the SmPC of the reference product RoActemra and Avtozma, physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with tocilizumab is currently unknown.

The benefits of an effective treatment with Avtozma outweigh the apparent risk of Demyelinating Disorders for which effective risk management strategies are available.

Important potential risk: Immunogenicity

Risk-benefit impact:

Immunogenic response to therapeutic molecules can generate anti-drug antibodies (ADAs), which can be either neutralising or non-neutralising. Neutralising antibodies bind to sites in therapeutic proteins in such a way that they directly impair or abrogate the biological functions of therapeutic proteins (Kuriakose et al., 2016).

In the clinical studies with the reference product RoActemra, the incidence of anti-drug antibodies to tocilizumab was low in patients with adult RA, pJIA, GCA, or sJIA. No correlation between the development of anti-tocilizumb antibodies and serious hypersensitivity or anaphylaxis was observed. (RoActemra RMP)

A total of 2,876 patients have been tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials with the reference product. Of 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.

The benefits of an effective treatment with Avtozma outweigh the apparent risk of immunogenicity for which effective risk management strategies are available.

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

Not applicable as this is an initial RMP.

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

Since Avtozma is a biosimilar medicine, all risks have been included based on the safety profile of the reference product RoActemra for all indications, RA, sJIA, pJIA, CRS, GCA and COVID-19.

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

Important identified risk: Serious infection (Medical Dictionary for Regulatory Activities [MedDRA] System Organ Class [SOC] Infections and Infestations)
The safety concern "serious infection" is an important identified risk for chronic Avtozma dosing, but is assessed as an important potential risk for the indication of COVID-19.

Potential mechanisms:

Patients with RA, GCA, pJIA, and sJIA are at a higher risk of infection than the general population because of altered immunological function as well as concomitant therapies used to treat the underlying disease (e.g., corticosteroids and immunomodulating agents). Biologic therapies have been shown to be associated with infections, particularly serious infections, including tuberculosis and opportunistic infections.

Patients with COVID-19 are at higher risk of secondary bacterial or fungal infection. Superinfections and co-infections are common in respiratory viral illnesses including COVID-19, particularly in severe hospitalised cases. Acute suppression of IL-6 may increase the infection risk due to IL-6's role in the acute-phase response and overall defence mechanism against infectious organisms.

Evidence source(s) and strength of evidence:

The risk of serious infections is increased in the RA patients being treated with Interleukin inhibitors (IL) and immunosuppressant like tocilizumab.

Serious infections, some with fatal outcomes have been reported in the clinical development programme of the reference product. The most commonly reported fatal infections were pneumonia and sepsis. Other reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections (e.g., candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii) pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis. Cases of opportunistic infections have been reported.

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
Total Number of TEAEs	5	5	0	0	4
Number of Patients with TEAEs [1]	5 (1.3%)	5 (2.1%)	0	0	4 (1.7%)
Incidence of TEAEs per 100PYs	1.916	2.415	0	0	2.601
95% CI for Incidence of TEAEs per 100PYs	(0.622, 4.471)	(0.784, 5.637)	(NE, 63.168)	(NE, 7.662)	(0.709, 6.659)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 26.0.
*Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
**TEAEs occurred during Treatment Period I in the switching arm is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
Abbreviation: CI = Confidence Interval; IV = Intravenous; NE = Not Estimated; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event

Frequency with Severity, Seriousness and Outcome:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Total Number of TEAEs	5	5	0	0	4
Number of Patients with TEAEs [1] n (%)	5 (1.3%)	5 (2.1%)	0	0	4 (1.7%)
95% CI for proportion of patients with TEAEs	(0.43, 3.07)	(0.70, 4.92)	(0.00, 10.58)	(0.00, 3.30)	(0.46, 4.26)
Severity/Nature of risk [2]					
Missing	0	0	0	0	0
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	4 (1.1%)	4 (1.7%)	0	0	3 (1.3%)
Grade 4	0	0	0	0	1 (0.4%)
Grade 5	1 (0.3%)	1 (0.4%)	0	0	0
Seriousness [3]					
Serious	5 (1.3%)	5 (2.1%)	0	0	4 (1.7%)
Non-serious	0	0	0	0	0

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Outcomes [4]					
Missing/Unknown	0	0	0	0	0
Recovered/Resolved, Recovered/Resolved with Sequelae	4 (1.1%)	4 (1.7%)	0	0	2 (0.8%)
Recovering/Resolving	0	0	0	0	2 (0.8%)
Not Recovered/Not Resolved	0	0	0	0	0
Fatal	1 (0.3%)	1 (0.4%)	0	0	0

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown/Missing
From the MedDRA dictionary, version 26.0.
Abbreviations: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** TEAEs occurred during Treatment Period 1 in the switching arm is included in this column.

Overall, there were eight (9) TEAEs in eight (9) patients related to serious infection; five (5) in the CT-P47 IV group, none in the CT-P47 SC and switched from reference product group, and four (4) in the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P47 IV group was 2.415 (95% CI: 0.784, 5.637), in the CT-P47 SC group was 0.000 (95% CI: NE, 63.168), in the switched from reference product group was 0.000 (95% CI: NE, 7.662), and in the reference product group was 2.601 (95% CI: 0.709, 6.659).

Four (4) patients from the CT-P47 IV group and three (3) patients from the reference product group reported Grade 3 events. One (1) patient reported Grade 4 and Grade 5 event in the reference product group and CT-P47 IV group per each.

In six (6) patients TEAEs related to serious infection were reported as “recovered/resolved, recovered/resolved with sequelae”, in two (2) patient it was reported as recovering/resolving and in one (1) patient it was reported as “fatal” at the end of the trial period.

The proportion of patients with TEAEs in the CT-P47 IV group was 2.1% (95% CI: 0.70, 4.92), in the CT-P47 SC group was 0 (95% CI: 0.00, 10.58), in the switched from reference product group was 0 (95% CI: 0.00, 3.30), and in the reference product group was 1.7% (95% CI: (0.46, 4.26).

Risk factors and risk groups:

Factors associated with the risk of serious infection are older age, lower annual income, higher comorbidity scores, pulmonary disease, higher disability and patient global assessment scores, being exposed to several csDMARDs previously, and higher weighted cumulative prednisone doses (Ozen et al., 2019).

Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with tocilizumab and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase with body weight. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes, or ILD which may predispose patients to infections).

Vigilance for timely detection of serious infections is recommended as signs and symptoms of acute inflammation may be lessened due to suppression of the acute-phase reactants.

Preventability:

The SmPC of the reference product RoActemra and Avtozma, contraindicates the use of tocilizumab in patients with active, severe infections. The treatment should be interrupted if the patient develops a serious infection until the infection is controlled. The SmPC warns that the 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 ILD) which may predispose patients to infections. The patients should be monitored for timely detection of serious infection.

Prescribing information and Patient Information Leaflet recommend the need for increased vigilance regarding infections (including screening for latent tuberculosis [TB]) and to administer prophylactic treatment with standard antibacterial therapy in patients with latent TB prior to start of treatment with tocilizumab.

Before initiating therapy in RA, sJIA, pJIA, and CRS (including screening for latent TB), COVID-19, the possibility of a serious infection should be ruled out.

The patients with COVID-19 are recommended to contact a healthcare professional immediately should they identify symptoms suggesting infection emergence to assure rapid evaluation and appropriate treatment.

Impact on the risk-benefit balance of the product:

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab. Patients may experience severe infection or frequent minor infections. There have been a number of serious infections reported with tocilizumab in RoActemra clinical studies, 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 Avtozma SmPC, Patient Information Leaflet, Patient Alert Card, Dosing Guide and the Educational Materials for Healthcare professionals and patients, will mitigate the risk and severity, and also provide information regarding managing the risk.

Public health impact:

The risk does not have an impact on public health.

Important identified risk: Complications of Diverticulitis (Standardised MedDRA Query [SMQ] GI Perforation SMQ)

The safety concern “complications of diverticulitis” is an important identified risk for chronic Avtozma dosing, but is assessed as an important potential risk for the indication of COVID-19.

Potential mechanisms:

Diverticulitis is considered to be an acute inflammation caused when the faecolith abrades the mucosa of the diverticular sac, causing inflammation and expansion of usual bacterial flora. Subsequently, bacteria may breach the mucosa and extend the process through the full wall thickness, where toxin production, gas production and the mucosal injury may ultimately lead to perforation.

Alternatively, trauma from a faecolith may cause irritation of the mucosa with low-grade inflammation, then vascular congestion and further obstruction of the diverticular tract leading to stool trapping and bacterial overgrowth, with purulent material forming inside the diverticular sac.

Another mechanism for development of diverticulitis could be a long-lasting (or recurrent) compression of vasa recta in the "neck" of the diverticulum due to a prolonged and/or marked contractile spike of the colon. Indeed, the tiny "neck" of the diverticulum passes through the circular muscle of the bowel wall and may be abnormally compressed, leading to mucosal ischaemia at the apex of the sac or even microperforation (Zullo et al., 2018).

Evidence source(s) and strength of evidence:

Diverticulosis is a clinical condition in which multiple sac-like protrusions (diverticula) develop along the weaker portions of the gastrointestinal tract, mainly in the large intestine (most commonly the sigmoid colon). The majority of individuals with diverticulosis are asymptomatic. Diverticulitis is the acute or chronic inflammation that may or may not be complicated by abscess formation, fistula formation, bowel obstruction, or perforation (Nallapeta et al., 2023).

Complications of diverticulitis have been reported in the clinical development programme of the reference product. Two events were fatal while most of the reported events resolved without consequences. Over half of the events involved diverticular perforation.

During the 6-month controlled clinical trials of the reference product, 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. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
Total Number of TEAEs	2	2	0	0	0
Number of Patients with TEAEs [1]	2 (0.5%)	2 (0.9%)	0	0	0
Incidence of TEAEs per 100PYs	0.766	0.966	0	0	0

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
95% CI for Incidence of TEAEs per 100PYs	(0.093, 2.768)	(0.117, 3.490)	(NE, 63.168)	(NE, 7.662)	(NE, 2.399)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 26.0.
*Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
**TEAEs occurred during Treatment Period I in the switching arm is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
Abbreviation: CI = Confidence Interval; IV = Intravenous; NE = Not Estimated; SC = Subcutaneous;
TEAE = Treatment Emergent Adverse Event

Frequency with Severity, Seriousness and Outcome:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Total Number of TEAEs	2	2	0	0	0
Number of Patients with TEAEs [1] n (%)	2 (0.5%)	2 (0.9%)	0	0	0
95% CI for proportion of patients with TEAEs	(0.06, 1.90)	(0.10, 3.05)	(0.00, 10.58)	(0.00, 3.30)	(0.00, 1.54)
Severity/Nature of risk [2]					
Missing	0	0	0	0	0
Grade 1	0	0	0	0	0
Grade 2	1 (0.3%)	1 (0.4%)	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Grade 5	1 (0.3%)	1 (0.4%)	0	0	0
Seriousness [3]					
Serious	1 (0.3%)	1 (0.4%)	0	0	0
Non-serious	1 (0.3%)	1 (0.4%)	0	0	0
Outcomes [4]					
Missing/Unknown	0	0	0	0	0
Recovered/Resolved, Recovered/Resolved with Sequelae	1 (0.3%)	1 (0.4%)	0	0	0

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Recovering/Resolving	0	0	0	0	0
Not Recovered/Not Resolved	0	0	0	0	0
Fatal	1 (0.3%)	1 (0.4%)	0	0	0

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown/Missing
From the MedDRA dictionary, version 26.0.
Abbreviations: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** TEAEs occurred during Treatment Period 1 in the switching arm is included in this column.

Overall, there were two (2) TEAEs in two (2) patients related to complications of diverticulitis, which were reported in the CT-P47 IV group; none was reported in the CT-P47 SC group, switched from the reference product group, and the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P47 IV group was 0.966 (95% CI: 0.117, 3.490), in the CT-P47 SC group was 0.000 (95% CI: NE, 63.168), in the switched from reference product group was 0.000 (95% CI: NE, 7.662), and in the reference product group was 0.000 (95% CI: NE, 2.399).

The one patient reporting complications of diverticulitis in the CT-P47 IV group was categorised as experiencing serious event with Grade 5 and it was reported as fatal at the end of the trial period. Another patient was categorised as experiencing non-serious event with Grade 2 and it was reported as recovered/resolved, recovered/resolve with sequelae

The proportion of patients with TEAEs in the CT-P47 IV group was 0.9% (95% CI: 0.10, 3.05), in the CT-P47 SC group was 0 (95% CI: 0.00, 10.58), in the switched from reference product group was 0 (95% CI: 0.00, 3.30), and in the reference product group was 0 (95% CI: (0.00, 1.54).

Risk factors and risk groups:

Patient with a previous history of intestinal ulceration or diverticulitis.

Preventability:

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

Impact on the risk-benefit balance of the product:

Although perforation of the large bowel has been reported in patients who had large bowel infection, it is an uncommon event and therefore, does not have an impact on the risk-benefit balance of Avtozma.

The Avtozma SmPC, Patient Information Leaflet, Patient Alert Card, Dosing Guide and Educational Materials for Healthcare professionals and patients, will mitigate the risk and severity and also provide information regarding managing the risk.

Public health impact:

Diverticulitis is an uncommon adverse event of tocilizumab therefore, there is no impact on public health.

Important identified risk: Neutropenia (MedDRA High-Level Term [HLT] Neutropenias MedDRA PT Neutrophil count decreased)

Potential mechanisms:

IL-6 blockade, directly or indirectly, may affect neutrophil apoptosis and removal from the circulation. Neutrophils express IL-6R, which could directly bind IL-6 blockers such as tocilizumab, to act as an opsonin and promote neutrophil phagocytosis by FcγR-expressing phagocytic cells.

Alternatively, tocilizumab bound to cell surface neutrophil IL-6R could trigger intracellular signalling pathways, leading to apoptosis. If neutrophils are dependent upon IL-6 for cell survival, then serum depletion by IL-6 blockers may increase their apoptosis in vivo, leading to decreased circulating levels. However, alternative explanations to explain TCZ-induced neutropenia are possible, e.g., by induction of margination. IL-6 administration in animals induces neutrophilia, via rapid mobilisation of neutrophils from the marginated pool into the circulating pool, followed by accelerated release of neutrophils from the bone marrow. Serum levels of IL-6 are elevated in RA patients, therefore decreases in circulating IL-6 following TCZ infusion may induce margination of neutrophils (Wright et al., 2014).

Evidence source(s) and strength of evidence:

Neutropenia is a condition where the body does not have enough neutrophils, an important type of white blood cells. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500/µL. Severe neutropenia is defined as less than 500/µL (AAAAI).

Neutropenia has been reported in the Clinical development programme of the reference product. There was a higher incidence of Grade 1 or 2 neutropenia among patients weighing less than < 60 kg compared with patients in higher body weight categories.

In the IV RA population in the reference product clinical studies, 250 of the 4163 patients developed grade 3 or 4 neutropenia. In the COVID-19 clinical studies (WA42380, WA42380 and WA42511 studies), 6 cases of Grade 4 neutropenia were reported amongst 724 patients treated with tocilizumab.

In the 6-month controlled trials with reference product decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/L did so within 8 weeks after starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs

Neutropenia associated with the use of tocilizumab in COVID-19 has been reported in scientific literature. 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).

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
Total Number of TEAEs	70	50	3	17	40
Number of Patients with TEAEs [1]	49 (13.0%)	32 (13.7%)	3 (9.1%)	14 (12.7%)	28 (11.8%)
Incidence of TEAEs per 100PYs	26.820	24.153	51.371	35.310	26.008
95% CI for Incidence of TEAEs per 100PYs	(20.908, 33.886)	(17.927, 31.843)	(10.594, 150.129)	(20.569, 56.535)	(18.581, 35.416)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 26.0.
*Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
**TEAEs occurred during Treatment Period I in the switching arm is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
TEAEs indicate the applicable risks in relevant tables.
Abbreviation: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event

Frequency with Severity, Seriousness and Outcome:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Total Number of TEAEs	70	50	3	17	40
Number of Patients with TEAEs [1] n (%)	49 (13.0%)	32 (13.7%)	3 (9.1%)	14 (12.7%)	28 (11.8%)
95% CI for proportion of patients with TEAEs	(9.77, 16.82)	(9.55, 18.75)	(1.92, 24.33)	(7.14, 20.43)	(8.00, 16.62)
Severity/Nature of risk [2]					

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Missing	0	0	0	0	0
Grade 1	16 (4.2%)	10 (4.3%)	0	6 (5.5%)	12 (5.1%)
Grade 2	15 (4.0%)	10 (4.3%)	1 (3.0%)	4 (3.6%)	4 (1.7%)
Grade 3	17 (4.5%)	11 (4.7%)	2 (6.1%)	4 (3.6%)	11 (4.6%)
Grade 4	1 (0.3%)	1 (0.4%)	0	0	1 (0.4%)
Grade 5	0	0	0	0	0
Seriousness [3]					
Serious	0	0	0	0	0
Non-serious	49 (13.0%)	32 (13.7%)	3 (9.1%)	14 (12.7%)	28 (11.8%)
Outcomes [4]					
Missing/Unknown	0	0	0	0	0
Recovered/Resolved, Recovered/Resolved with Sequelae	43 (11.4%)	28 (12.0%)	2 (6.1%)	13 (11.8%)	26 (11.0%)
Recovering/Resolving	4 (1.1%)	3 (1.3%)	0	1 (0.9%)	0
Not Recovered/Not Resolved	2 (0.5%)	1 (0.4%)	1 (3.0%)	0	2 (0.8%)
Fatal	0	0	0	0	0

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown/Missing
From the MedDRA dictionary, version 26.0.
Abbreviations: CI = Confidence Interval; TEAE = Treatment Emergent Adverse Event; IV = Intravenous; SC = Subcutaneous
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** TEAEs occurred during Treatment Period 1 in the switching arm is included in this column.

Overall, there were 110 TEAEs in 77 patients related to neutropenia; 50 in the CT-P47 IV group, three (3) in the CT-P47 SC group, seventeen (17) in switched from reference product group, and 40 in the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P47 IV group was 24.153 (95% CI: 17.927, 31.843), in the CT-P47 SC group was 51.371 (95% CI: 10.594, 150.129), in the switched from reference product group was 35.310 (95% CI: 20.569, 56.535), and in the reference product group was 26.008 (95% CI: 18.581, 35.416).

All patients (32 patients [13.7%] in the CT-P47 IV group, three (3) patients [9.1%] in the CT-P47 SC group, fourteen (14) patients [12.7%] in the switched from reference product group and 28 patients [11.8%] in the reference product group) were categorised as experiencing non-serious events.

Ten (10) patients from the CT-P47 IV group, six (6) patients from the switched from reference product group and 12 patients from the reference product group reported Grade 1 events. Ten (10) patients from the CT-P47 IV group, one (1) patient from CT-P47 SC group, four (4) patients from the switched from reference product group and four (4) patients from the reference product group reported Grade 2 events. Eleven (11) patients from the CT-P47 IV group, two (2) patients from CT-P47 SC group, four (4) patients from the switched from reference product group and 11 patients from the reference product group reported Grade 3 events. One (1) patient from the CT-P47 IV group and one (1) patient from the reference product group reported Grade 4 event.

In 69 patients TEAEs related to neutropenia were reported as “recovered/resolved, recovered/resolved with sequelae”, in four (4) patient it was reported as recovering/resolving and in four (4) patients it was reported as “not recovered/no resolved” at the end of the trial period.

The proportion of patients with TEAEs in the CT-P47 IV group was 13.7% (95% CI: 9.55, 18.75), in the CT-P47 SC group was 9.1% (95% CI: 1.92, 24.33), in the switched from reference product group was 12.7% (95% CI: 7.14, 20.43), and in the reference product group was 11.8% (95% CI: 8.00, 16.62).

Risk factors and risk groups:

Not identified.

Preventability:

In patients not previously treated with tocilizumab, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L. In patients who develop an ANC < 0.5 x 10^9/L or a platelet count < 50 x 10^3/μL, 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. Monitoring of neutrophil counts according to current standard clinical practices is recommended for patients with COVID-19.

Impact on the risk-benefit balance of the product:

Neutropenia has been commonly reported in association with tocilizumab treatment. The Avtozma SmPC, Patient Information Leaflet, Dosing Guide and Educational Materials for Healthcare professionals and patients provide information on management of the important identified risk and the risk mitigation measures.

Public health impact:

Based on currently available data and preventability, no public health impact in terms of risk to the treated population has been identified.

Important identified risk: Hepatotoxicity (MedDRA 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:

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 Tumour Necrosis factor (TNF)α. 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:

Tocilizumab commonly causes mild serum liver enzyme elevations that are usually short lived and asymptomatic, but has also been linked to rare instances of clinically apparent liver injury with jaundice, and occasional reactivation of hepatitis B (LiverTox, 2021).

In the clinical development programme of the reference product, mild and moderate elevations of liver enzymes have been observed with tocilizumab treatment. Increased frequency of these elevations was observed when drugs, which are known to cause liver toxicity (e.g., methotrexate), were used in combination with tocilizumab.

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				**Tocilizumab IV reference product** (N=237)**
	Total (N=377)	**CT-P47 IV (N=234)**	**CT-P47 SC (N=33)**	**Switched from Tocilizumab IV reference product* (N=110)**	
Total Number of TEAEs	205	163	1	41	143
Number of Patients with TEAEs [1]	107 (28.4%)	81 (34.6%)	1 (3.0%)	25 (22.7%)	82 (34.6%)
Incidence of TEAEs per 100PYs	78.545	78.740	17.124	85.159	92.980

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
95% CI for Incidence of TEAEs per 100PYs	(68.160, 90.065)	(67.116, 91.798)	(0.434, 95.408)	(61.112, 115.528)	(78.366, 109.529)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 26.0.
*Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
**TEAEs occurred during Treatment Period I in the switching arm is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
Abbreviation: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event

Frequency with Severity, Seriousness and Outcome:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Total Number of TEAEs	205	163	1	41	143
Number of Patients with TEAEs [1] n (%)	107 (28.4%)	81 (34.6%)	1 (3.0%)	25 (22.7%)	82 (34.6%)
95% CI for proportion of patients with TEAEs	(23.88, 33.22)	(28.54, 41.09)	(0.08, 15.76)	(15.28, 31.70)	(28.56, 41.03)
Severity/Nature of risk [2]					
Missing	0	0	0	0	0
Grade 1	54 (14.3%)	38 (16.2%)	0	16 (14.5%)	43 (18.1%)
Grade 2	47 (12.5%)	37 (15.8%)	1 (3.0%)	9 (8.2%)	35 (14.8%)
Grade 3	6 (1.6%)	6 (2.6%)	0	0	4 (1.7%)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Seriousness [3]					
Serious	0	0	0	0	0
Non-serious	107 (28.4%)	81 (34.6%)	1 (3.0%)	25 (22.7%)	82 (34.6%)
Outcomes [4]					
Missing/Unknown	0	0	0	0	1 (0.4%)
Recovered/Resolved, Recovered/Resolved with Sequelae	57 (15.1%)	43 (18.4%)	1 (3.0%)	13 (11.8%)	56 (23.6%)
Recovering/Resolving	26 (6.9%)	17 (7.3%)	0	9 (8.2%)	13 (5.5%)
Not Recovered/Not Resolved	24 (6.4%)	21 (9.0%)	0	3 (2.7%)	12 (5.1%)

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Fatal	0	0	0	0	0

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown/Missing
From the MedDRA dictionary, version 26.0.
Abbreviations: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** TEAEs occurred during Treatment Period 1 in the switching arm is included in this column.

Overall, there were 348 TEAEs in 189 patients related to hepatotoxicity; 163 in the CT-P47 IV group, one (1) in the CT-P47 SC group, 41 in switched from reference product group, and 143 in the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P47 IV group was 78.740 (95% CI: 67.116, 91.798), in the CT-P47 SC group was 17.124 (95% CI: 0.434, 95.408), in the switched from reference product group was 85.159 (95% CI: 61.112, 115.528), and in the reference product group was 92.980 (95% CI: 78.366, 109.529).

All patients (81 patients [34.6%] in the CT-P47 IV group, one (1) patient [3.0%] in the CT-P47 SC group, 25 patients [22.7%] in the switched from reference product group and 82 patients [34.6%] in the reference product group) were categorised as experiencing non-serious events.

Thirty eight (38) patients from the CT-P47 IV group, sixteen (16) patients from the switched from reference product group and 43 patients from the reference product group reported Grade 1 events. Thirty seven (37) patients from the CT-P47 IV group, one (1) patient from CT-P47 SC group, nine (9) patients from the switched from reference product group and 35 patients from the reference product group reported Grade 2 events. Four (6) patients from the CT-P47 IV groupand three (4) patients from the reference product group reported Grade 3 events.

In 113 patients TEAEs related to hepatotoxicity were reported as “recovered/resolved, recovered/resolved with sequelae”, in thirty nine (39) patient it was reported as recovering/resolving and in thirty six (36) patients it was reported as “not recovered/not resolved” at the end of the trial period.

The proportion of patients with TEAEs in the CT-P47 IV group was 34.6% (95% CI: 28.54, 41.09), in the CT-P47 SC group was 3.0% (95% CI: 0.08, 15.76), in the switched from reference product group was 22.7% (95% CI: 15.28, 31.70), and in the reference product group was 34.6% (95% CI: 28.56, 41.03).

Risk factors and risk groups:

Patient with 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., may impact individual background risk.

Patients with COVID-19 frequently experience hepatic injury of various degrees (Saha et al., 2022).

Treatment with other hepatotoxic drugs (e.g., MTX).

Preventability:

Treatment with Avtozma, particularly when administered concomitantly with methotrexate, 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.

Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated ALT or AST > 1.5 x ULN. In RA, pJIA and sJIA patients with baseline ALT or AST > 5 x ULN, treatment is not recommended.

In 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. For ALT or AST elevations > 3–5 x ULN, confirmed by repeat testing, tocilizumab treatment should be interrupted.

In patients with COVID-19, monitoring of ALT/AST according to current standard clinical practices is recommended. In patients with COVID-19 with elevated ALT or AST > 10 x ULN, initiation of treatment with tocilizumab is not recommended.

Impact on the risk-benefit balance of the product:

This important identified risk does not have an impact on the positive risk-benefit balance of the tocilizumab. The Avtozma SmPC, Patient Information Leaflet, Patient Alert Card and Educational Materials for Healthcare professionals and patients will mitigate the risk and severity, and also provide information regarding managing the risk.

Public health impact:

The frequency of the observed serious hepatotoxicity events is considered rare therefore, no potential public health impact has been identified.

Important potential risk: Thrombocytopenia and the Potential Risk of Bleeding (MedDRA SMQ Haematopoietic thrombocytopenia)

Potential mechanisms:

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

Evidence source(s) and strength of evidence:

Thrombocytopenia is the condition characterised by a platelet count below the lower limit of normal for adults, i.e., 150 x 10^3/µL. Platelets are blood cells that help in blood clotting and wound healing risks associated with thrombocytopenia range from no risk at all to bleeding risks and thrombosis. The correlation between severity of thrombocytopenia and bleeding risk is uncertain. (Jinna et al., 2023).

In the clinical studies with reference product, 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.

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
Total Number of TEAEs	29	27	1	1	15
Number of Patients with TEAEs [1]	17 (4.5%)	15 (6.4%)	1 (3.0%)	1 (0.9%)	9 (3.8%)
Incidence of TEAEs per 100PYs	11.111	13.043	17.124	2.077	9.753
95% CI for Incidence of TEAEs per 100PYs	(7.441, 15.958)	(8.595, 18.977)	(0.434, 95.408)	(0.053, 11.573)	(5.459, 16.086)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 26.0.
*Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
**TEAEs occurred during Treatment Period I in the switching arm is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25

Abbreviation: CI = Confidence Interval; NE = Not Estimated; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event

Frequency with Severity, Seriousness and Outcome:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Total Number of TEAEs	29	27	1	1	15
Number of Patients with TEAEs [1] n (%)	17 (4.5%)	15 (6.4%)	1 (3.0%)	1 (0.9%)	9 (3.8%)
95% CI for proportion of patients with TEAEs	(2.65, 7.12)	(3.63, 10.35)	(0.08, 15.76)	(0.02, 4.96)	(1.75, 7.09)
Severity/Nature of risk [2]					
Missing	0	0	0	0	0
Grade 1	10 (2.7%)	9 (3.8%)	0	1 (0.9%)	6 (2.5%)
Grade 2	7 (1.9%)	6 (2.6%)	1 (3.0%)	0	3 (1.3%)
Grade 3	0	0	0	0	0

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Seriousness [3]					
Serious	0	0	0	0	0
Non-serious	17 (4.5%)	15 (6.4%)	1 (3.0%)	1 (0.9%)	9 (3.8%)
Outcomes [4]					
Missing/Unknown	0	0	0	0	0
Recovered/Resolved, Recovered/Resolved with Sequelae	12 (3.2%)	10 (4.3%)	1 (3.0%)	1 (0.9%)	5 (2.1%)
Recovering/Resolving	0	0	0	0	2 (0.8%)
Not Recovered/Not Resolved	5 (1.3%)	5 (2.1%)	0	0	2 (0.8%)
Fatal	0	0	0	0	0

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown/Missing
From the MedDRA dictionary, version 26.0.
Abbreviations: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event;
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** TEAEs occurred during Treatment Period 1 in the switching arm is included in this column.

Overall, there were 44 TEAEs in 26 patients related to thrombocytopenia and the potential risk of bleeding; 15 in the CT-P47 IV group, one (1) in the CT-P47 SC group, one (1) in switched from reference product group, and nine (9) in the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P47 IV group was 13.043 (95% CI: 8.595, 18.977), in the CT-P47 SC group was 17.124 (95% CI: 0.434, 95.408), in the switched from reference product group was 2.077 (95% CI: 0.053, 11.573), and in the reference product group was 9.753 (95% CI: 5.459, 16.086).

All patients (15 patients [6.4%] in the CT-P47 IV group, one (1) patients [3.0%] in the CT-P47 SC group, one (1) patients [3.0%] in the switched from reference product group and nine (9) patients [3.8%] in the reference product group) were categorised as experiencing non-serious events.

Nine (9) patients from the CT-P47 IV group, one (1) patient from the switched group and six (6) patients from the reference product group reported Grade 1 events. Six (6) patients from the CT-P47 IV group, one (1) patient from CT-P47 SC group and three (3) patients from the reference product group reported Grade 2 events.

In 17 patients TEAEs related to thrombocytopenia and the potential risk of bleeding were reported as "recovered/resolved, recovered/resolved with sequelae", in two (2) patients it was reported as recovering/resolving and in seven (7) patients it was reported as "not recovered/not resolved" at the end of the trial period.

The proportion of patients with TEAEs in the CT-P47 IV group was 6.4% (95% CI: 3.63, 10.35), in the CT-P47 SC group was 3.0% (95% CI: 0.08, 15.76), in the switched from reference product group was 0.9% (95% CI: 0.02, 4.96), and in the reference product group was 3.8% (95% CI: 1.75, 7.09).

Risk factors and risk groups:

Advanced patient age and a low platelet count prior to tocilizumab treatment were associated with the development of thrombocytopenia after treatment (Lee et al., 2019).

Preventability:

Caution should be exercised when considering initiation of tocilizumab treatment in patients with a low platelet count (i.e., platelet count below 100 x 10^3/ µL. Treatment should be discontinued if the patient develops a platelet count < 50 x 10^3/ µL.

In RA patients, platelets should be monitored 4 to 8 weeks after 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. In COVID-19 patients platelet counts should be monitored according to current standard clinical practices.

Impact on the risk-benefit balance of the product:

This important potential risk does not have an impact on the positive risk-benefit balance of tocilizumab. The Avtozma SmPC, Patient Information Leaflet and Educational Materials for Healthcare professionals and patients will mitigate the risk and severity, and also provide information regarding managing the risk.

Public health impact:

No public health impact has been identified.

Important potential risks: Elevated Lipid Levels and Potential Risk of Cardiovascular and Cerebrovascular Events (MedDRA SMQ Dyslipidemia SMQ, Myocardial infarction SMQ narrow, Ischaemic central nervous system vascular conditions SMQ narrow, Haemorrhagic central nervous system vascular condition SMQ narrow)

Potential mechanisms:

Theoretically, IL-6 is a cytokine that plays an important role in autoimmune and inflammatory regulation, and its level is directly correlated to insulin resistant and free fatty acid by increasing the adipocyte lipolysis of triglycerides. Given that tocilizumab is an IL-6 inhibitor which blocks the IL-6 receptor, it was found that IL-6 levels appear to be increased after treatment, which suggests that the mechanism underlying dyslipidaemia is due to the direct effect of IL-6 (Alsulaim et al., 2021).

Although the precise mechanisms remain to be established, cytokine-induced activation of the reticuloendothelial system is potentially critical to such changes. This association could be attributed to the fact that treatment with biologic DMARDs is known to effectively reduce the inflammatory state, which in turn leads to a paradoxical elevation of cholesterol levels in response to their anti-inflammatory effect (Choy et al., 2009).

Evidence source(s) and strength of evidence:

Elevated levels of blood lipids are well documented risk factors for cardiovascular disease. The problem can be due solely to hereditary factors, but more commonly it is an acquired condition (Nelson, 2013).

In the clinical studies with the reference product, increases in total cholesterol, low density lipoprotein (LDL), and triglyceride levels have been observed in patients following treatment with tocilizumab. The relationship of these elevations and the risk for cardiovascular/cerebrovascular disease is unknown.

Characterisation of the risk:

There were no TEAEs reported for elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events in the CT-P47 IV group (234 patients), CT-P47 SC group (33 patients), switched from reference product group (110 patients), and the reference product group (237 patients) in Studies CT-P47 3.1/3.2.

Risk factors and risk groups:

None identified

Preventability:

Lipid parameters should be measured 4 to 8 weeks after the initiation of tocilizumab therapy and patients should be managed according to local clinical guidelines for management of hyperlipidaemia. Patients with RA are at an increased risk for cardiovascular disorders and therefore the risk factors (e.g. hypertension, hyperlipidaemia) should be managed as part of usual standard of care.

Impact on the risk-benefit balance of the product:

The Avtozma SmPC, Patient Information Leaflet, Dosing Guide and Educational Materials for Healthcare professionals and patients will mitigate the risk and severity, and also provide information regarding managing the risk. Therefore, this important potential risk does not have an impact on the positive risk-benefit balance of the tocilizumab.

Public health impact:

Cardiovascular and cerebrovascular complications are observed at a low frequency in patients treated with Avtozma, therefore, the public health impact in terms of risk to the treated population remains minimal.

Important potential risks: Malignancies (MedDRA SMQ Malignancies SMQ narrow)

Potential mechanisms:

Tocilizumab is an immunosuppressive agent and may therefore result in an increased risk of malignancy.

Systemic inflammation in RA is associated with increased risk for malignancy. IL-6 is an inflammatory cytokine involved in local and systemic manifestations of RA and is implicated in the growth and transformation of multiple myeloma and ovarian, lung, bladder, breast, colon and prostate cancers. IL-6 transgenic mice develop transplantable monoclonal plasmacytomas, akin to multiple myeloma in humans, and IL-6 is involved in the growth of human myeloma and human renal carcinoma cells *in-vitro* (Rubbert-Roth et al., 2016).

Evidence source(s) and strength of evidence:

According to published scientific literature evidence, patients with rheumatoid arthritis (RA) are at similar risk for most types of malignancies compared with the general population; however, they are at increased risk for certain anatomical site-specific malignancies, such as lymphoma and lung cancer, and may even be at increased risk for skin cancer, particularly non-melanoma skin cancer (NMSC). Large epidemiological studies show that risk for lung malignancy is estimated to be 20-80% higher, risk for lymphoma is approximately twice as high and risk for NMSC is 60-90% higher in patients with RA compared with the general population. Some observational and clinical trial data failed to demonstrate an increased risk of malignancies (Rubbert-Roth et al., 2016).

In the clinical studies with reference product, the rates and types of malignancies observed in the IV and SC tocilizumab populations were consistent over time. The incidence rates of malignancies in the IV RA and SC RA all exposure population were 1.26 (95% CI: 1.09, 1.44) and 1.24 events per 100 PY (95% CI: 0.76, 1.92) events per 100 PY, respectively.

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
Total Number of TEAEs	0	0	0	0	1
Number of Patients with TEAEs [1]	0	0	0	0	1 (0.4%)
Incidence of TEAEs per 100PYs	0	0	0	0	0.650

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product* (N=110)	
95% CI for Incidence of TEAEs per 100PYs	(NE, 1.413)	(NE, 1.782)	(NE, 63.168)	(NE, 7.662)	(0.016, 3.623)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 26.0.
*Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
**TEAEs occurred during Treatment Period I in the switching arm is included in this column.
Patient Year (PY) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
Abbreviation: CI = Confidence Interval; IV = Intravenous; NE = Not Estimated; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event

Frequency with Severity, Seriousness and Outcome:

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Total Number of TEAEs	0	0	0	0	1
Number of Patients with TEAEs [1] n (%)	0	0	0	0	1 (0.4%)
95% CI for proportion of patients with TEAEs	(0.00, 0.97)	(0.00, 1.56)	(0.00, 10.58)	(0.00, 3.30)	(0.01, 2.33)
Severity/Nature of risk [2]					
Missing	0	0	0	0	0
Grade 1	0	0	0	0	0
Grade 2	0	0	0	0	0
Grade 3	0	0	0	0	1 (0.4%)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Seriousness [3]					
Serious	0	0	0	0	1 (0.4%)
Non-serious	0	0	0	0	0
Outcomes [4]					
Missing/Unknown	0	0	0	0	0
Recovered/Resolved, Recovered/Resolved with Sequelae	0	0	0	0	1 (0.4%)
Recovering/Resolving	0	0	0	0	0

INDICATION: Rheumatoid Arthritis (CT-P47 3.1/3.2)					
	CT-P47				Tocilizumab IV reference product ** (N=237)
	Total (N=377)	CT-P47 IV (N=234)	CT-P47 SC (N=33)	Switched from Tocilizumab IV reference product * (N=110)	
Not Recovered/Not Resolved	0	0	0	0	0
Fatal	0	0	0	0	0

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Severity of outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown/Missing
From the MedDRA dictionary, version 26.0.
Abbreviations: CI = Confidence Interval; IV = Intravenous; SC = Subcutaneous; TEAE = Treatment Emergent Adverse Event
Confidence interval for proportion of patients with TEAEs is calculated using the Clopper-Pearson method.

* Patients assigned to the switching arm switched from reference product to CT-P47 IV after completion of Week 20.
** TEAEs occurred during Treatment Period 1 in the switching arm is included in this column..

Overall, there was one (1) TEAE in one (1) patient related to malignancies reported in the reference product group; none was reported in the CT-P47 IV group, CT-P47 SC group and switched from the reference product group. The incidence of TEAEs per 100 patient-years in the CT-P47 IV group was 0.000 (95% CI: NE, 1.782), in the CT-P47 SC group was 0.000 (95% CI: NE, 63.168), in the switched from reference product group was 0.000 (95% CI: NE, 7.662), and in the reference product group was 0.650 (95% CI: 0.016, 3.623).

The one (1) patient (0.4%) in the reference product group was categorised as experiencing serious event with Grade 3 and it was reported as recovered at the end of the trial period.

The proportion of patients with TEAEs in the CT-P47 IV group was 0 (95% CI: 0.00, 1.56), in the CT-P47 SC group was 0 (95% CI: 0.00, 10.58), in the switched from reference product group was 0 (95% CI: 0.00, 3.30), and in the reference product group was 0.4% (95% CI: 0.01, 2.33).

Risk factors and risk groups:

The risk for malignancy, including haematological malignancy, is potentially greater in patients with RA who use immunosuppressive agents (Rubbert-Roth et al., 2016).

Preventability:

The underlying mechanisms causing development of malignancies are not yet completely understood and thus, no preventive measure is currently known.

Impact on the risk-benefit balance of the product:

There have been very few reports of cancer, and no individual tumour type predominates. Despite the low event rate, a potential risk cannot be excluded. Avtozma treatment should not be initiated in subjects with cancer. The Avtozma SmPC, Patient Information Leaflet, Dosing Guide and Educational Materials for Healthcare professionals and patients, mitigate the risk severity and also provide information regarding managing the risk.

The available cumulative information does not provide evidence for an increased risk of malignancies in patients treated with tocilizumab. The benefits of an effective treatment with Avtozma outweigh the risk of malignancies.

Public health impact:

The risk of malignancy is known to be increased in patients with RA and with some treatments commonly used in RA, such as methotrexate and biologic DMARDs. A Food and Drug Administration (FDA) alert was published requiring the manufacturers of TNF blockers to update the Boxed Warning in the prescribing information to alert healthcare professionals of an increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers. EMEA 2010 priorities also identified the risk of malignancy as one of the potential long-term adverse effects of immunomodulators, including the anti-TNFs, rituximab, and tocilizumab.

Concern is high because of the seriousness of the risk; however, the public health impact is considered low because of the low frequency of such events.

Important potential risks: Demyelinating Disorders (MedDRA SMQ Demyelination SMQ narrow)

Potential mechanisms:

No exact potential mechanism for the development of Demyelinating Disorders has been identified.

Evidence source(s) and strength of evidence:

The demyelinating diseases are common neurological disorders that affect the central nervous system (CNS) and peripheral nervous system. They cause substantial disability and some are associated with a high mortality rate if not treated promptly (Javed et al., 2009).

In the clinical development programme of the reference product, there have been very few reports of nerve damage (demyelination) in patients treated with tocilizumab.

Characterisation of the risk:

There were no TEAEs reported for demyelinating disorders in the CT-P47 IV group (234 patients), CT-P47 SC group (33 patients), switched from reference product group (110 patients), and the reference product group (237 patients) in Study CT-P47 3.1/3.2.

Risk factors and risk groups:

None identified.

Preventability:

The underlying mechanisms causing development of demyelinating disorders are not yet completely understood and thus, no preventive measure is currently known.

Impact on the risk-benefit balance of the product:

There have been very few reports of demyelinating disorders in patients treated with tocilizumab, although the risk is unknown. The Avtozma SmPC, Patient Information Leaflet, and Educational Material for Healthcare professionals, will mitigate the risk and severity and also provide information regarding managing the risk.

Public health impact:

Not applicable.

Important potential risks: Immunogenicity (MedDRA PT Drug specific antibody, PT Drug specific antibody present)

Potential mechanisms:

Immunogenicity is caused by the response to the infusion or injection of a protein (IgG). The immune system can generate antibodies to therapeutic proteins by two general mechanisms: one relies on T cell co-stimulation of B cells while the other is independent of T cell.

Evidence source(s) and strength of evidence:

Immunogenicity is caused when a drug is detected by the body's immune system as a foreign substance and the body then elicits an immune response to the drug. (Gunn et al, 2016).

In the clinical studies of the reference product, positive anti-tocilizumab antibodies were detected using confirmation assay. In the IV RA all exposure population, a total of 44 of 3945 patients tested positive for anti-tocilizumab antibodies, 5 of whom also experienced a serious hypersensitivity reaction. Of the 1462 patients in the SC all exposure population who were tested for anti-tocilizumab antibodies, 20 (1.4%) patients developed anti-tocilizumab antibodies.

Characterisation of the risk:

There were no TEAEs reported for immunogenicity in the CT-P47 IV group (234 patients), CT-P47 SC group (33 patients), switched from reference product group (110 patients), and the reference product group (237 patients) in Studies CT-P47 3.1/3.2.

In study CT-P47 3.1, 2 (0.9%) patients in the CT-P47 maintenance group, no patient in the reference product maintenance group, and 3 (2.7%) patients in the switched to CT-P47 group had positive ADA results at Week 52 (EOS). Of the patients with positive ADA results at Week 52 (EOS), no patient in the CT-P47 maintenance, RoActemra maintenance, and switched to CT-P47 groups, respectively, was also positive for neutralising antibodies.

In the CT-P47 3.2 study, 1 (3.0%) patient had positive ADA test result at Week 0 (Day 1) prior to study drug administration. However, this patient did not show positive ADA test results in post-treatment visits until EOS. Two (6.1%) patients had positive ADA test results in post-treatment visits until EOS and were also positive for neutralising antibodies results.

Risk factors and risk groups:

None identified.

Preventability:

Not known.

Impact on the risk-benefit balance of the product:

The incidence of ADAs to tocilizumab is low in patients with adult RA, pJIA, GCA, or sJIA. No correlation between the development of anti-tocilizumab antibodies and the safety and efficacy response to tocilizumab has been observed in clinical trials with the reference product RoActemra.

Public health impact:

Not applicable.

SVII.3.2 Presentation of the missing information

There is no missing information available for inclusion in the list of safety concerns in the RMP.

Part II: Module SVIII - Summary of the safety concerns

Table 8: Summary of safety concerns

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

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Targeted follow-up questionnaires will be used for serious adverse events of the risks listed below:

- Serious infections[1]
- Complications of diverticulitis (including GI perforation)
- Thrombocytopenia and the potential risk of bleeding
- Hepatotoxicity
- Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events
- Malignancies
- Demyelinating disorders

Detailed forms for each risk are provided in the Annex 4.

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

Not applicable as there are no additional pharmacovigilance activities planned for Avtozma.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable, since no additional pharmacovigilance studies/activities are being conducted or planned.

[1] Routine pharmacovigilance Targeted follow-up questionary for events of special interest will collect neutrophil data in cases of serious infection.

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable, since there are no post authorisation efficacy studies planned for Avtozma

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

V.1 Routine Risk Minimisation Measures

Table 9: Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious Infections*	Routine risk communication: SmPC sections 4.3, 4.4, and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Complications of Diverticulitis*	Routine risk communication: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Neutropenia	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8. PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Hepatotoxicity	Routine risk communication:

	SmPC sections 4.2, 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: In patients with RA, GCA, pJIA, sJIA, ALT, and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Thrombocytopenia and the potential risk of bleeding	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Elevated Lipid Levels and Potential Risk of Cardiovascular /Cerebrovascular Events	Routine risk communication: SmPC sections 4.4 and 4.8. PIL sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Malignancies	Routine risk communication: SmPC sections 4.4 and 4.8. PIL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information:

	Legal status: Prescription only medicine
Demyelinating Disorders	Routine risk communication: SmPC section 4.4. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine
Immunogenicity	Routine risk communication: SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Prescription only medicine

V.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are targeted for the indications of RA, GCA, pJIA, and sJIA. CRS, an acute life-threatening condition treated in the hospital setting by oncologists, has a different benefit-risk profile relative to other indications. Given this therapeutic context, no additional risk minimisation measure is required for treatment of CRS. Use of tocilizumab for CRS and its risk profile are specified in the SmPC. The additional risk minimisation measures listed in Table 10 are not applicable for the COVID-19 indication.

Table 10: Part V.2: Additional Risk Minimisation Measures

Safety Concern	**Serious Infections ***
Additional Risk Minimisation 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 minimisation Activity	Patient Alert Card To inform both the patient and health care providers that TCZ increases the risk of developing 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	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Complications of Diverticulitis ***
Additional Risk Minimisation 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 complications of diverticulitis
Rationale for the additional risk minimisation Activity	Patient Alert Card To inform both the patient and health care providers that patients using TCZ may develop complications of diverticulitis which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of such events Patient Brochure To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL

	Healthcare Provider Brochure To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis Dosing Guide To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Neutropenia**
Additional Risk Minimisation 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 health care providers are aware of the need for timely and appropriate measures to diagnose and treat neutropenia
Rationale for the additional risk minimisation Activity	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 more detailed 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 Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety

	concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Hepatotoxicity**
Additional Risk Minimisation Measure	Patient Alert Card; Patient Brochure; Healthcare Provider Brochure;
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 detect hepatotoxicity
Rationale for the additional risk minimisation Activity	Patient Brochure To inform the patient of the risk of hepatotoxicity and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of hepatotoxicity Patient Alert Card To inform both the patient and health care providers that patients using TCZ may develop hepatotoxicity, and on rare occasions, patients have experience serious life-threatening liver problems, some of which have required liver transplant. Patients will be monitored closely for changes in blood liver enzyme level.
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Thrombocytopenia and the potential risk of bleeding**
Additional Risk Minimisation Measure	Patient Brochure; Healthcare Provider Brochure;
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 thrombocytopenia

Rationale for the additional risk minimisation Activity	Healthcare Provider Brochure To inform and provide more detailed 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 Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events**
Additional Risk Minimisation 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 health care providers are aware of the need for timely and appropriate measures to detect elevated lipid levels and evaluate further
Rationale for the additional risk minimisation Activity	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 more detailed 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	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety

	concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Malignancies**
Additional Risk Minimisation 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 health care providers are aware of the need for timely and appropriate measures to diagnose and treat malignancies
Rationale for the additional risk minimisation Activity	Patient Brochure To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of malignancies Dosing Guide To provide support to the healthcare provider regarding dosing and administration instructions and the risks
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.
Safety Concern	**Demyelinating Disorders**
Additional Risk Minimisation 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 minimisation Activity	Healthcare Provider Brochure To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Target audience and	Healthcare providers

planned distribution path	
Plans for evaluating the effectiveness of the interventions and criteria for success	Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Effectiveness will be assessed using postmarket reporting frequency of each safety concern as an outcome indicator. The occurrence of each safety concern will be monitored by routine pharmacovigilance activities. Data on the effectiveness of the additional risk minimisation activity will be presented in each scheduled PSUR for tocilizumab.

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

V.3 Summary of risk minimisation measures

Table 11: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious Infections*	Routine risk minimisation measures: SmPC sections 4.3, 4,4, and 4.8 PIL sections 2 and 4. Legal status: 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: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Complications of Diverticulitis*	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PIL sections 2 and 4. Legal status: 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: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Neutropenia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PIL section 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Hepatotoxicity	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PIL sections 2 and 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Alert Card Patient Brochure Healthcare Provider Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thrombocytopenia and the potential risk of bleeding	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Elevated Lipid Levels and Potential Risk of Cardiovascular /Cerebrovascular Events	Routine risk minimisation measures: SmPC sections 4.4, and 4.8 PIL sections 2 and 4. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Malignancies	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PIL section 2. Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Demyelinating Disorders	Routine risk minimisation measures: SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: Healthcare Provider Brochure	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC section 4.8 Legal status: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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

Part VI: Summary of the risk management plan

Summary of risk management plan for Avtozma (tocilizumab biosimilar)

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

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

This summary of the RMP for Avtozma should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Avtozma's RMP.

I. The medicine and what it is used for

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

Further information about the evaluation of Avtozma benefits can be found in Avtozma EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/avtozma.

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

Important risks of Avtozma, together with measures to minimise such risks and the proposed studies for learning more about Avtozma'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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (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 Avtozma 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 Avtozma. 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

Important identified risk: Serious infection*	
Evidence for linking the risk to medicine	The risk of serious infections is increased in the RA patients being treated with Interleukin inhibitors (IL) and immunosuppressant like tocilizumab. Serious infections, some with fatal outcomes have been reported in the clinical development programme of the reference product. The most commonly reported fatal infections were pneumonia and sepsis. Other reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections (e.g., candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii) pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis. Cases of opportunistic infections have been reported.
Risk factors and risk groups	Factors associated with the risk of serious infection are older age, lower annual income, higher comorbidity scores, pulmonary disease, higher disability and patient global assessment scores, being exposed to several csDMARDs previously, and higher weighted cumulative prednisone doses (Ozen et al., 2019). Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with tocilizumab and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase with body weight. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes, or ILD which may predispose patients to infections). Vigilance for timely detection of serious infections is recommended as signs and symptoms of acute inflammation may be lessened due to suppression of the acute-phase reactants.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.3, 4,4, and 4.8 PIL sections 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide
Important identified risk: Complications of diverticulitis*	
Evidence for linking the risk to medicine	Diverticulosis is a clinical condition in which multiple sac-like protrusions (diverticula) develop along the weaker portions of the gastrointestinal tract, mainly in the large intestine (most commonly the sigmoid colon). The majority of individuals with diverticulosis are asymptomatic. Diverticulitis is the acute or

	chronic inflammation that may or may not be complicated by abscess formation, fistula formation, bowel obstruction, or perforation (Nallapeta et al., 2023). Complications of diverticulitis have been reported in the clinical development programme of the reference product. Two events were fatal while most of the reported events resolved without consequences. Over half of the events involved diverticular perforation. During the 6-month controlled clinical trials of the reference product, 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. Reports of gastrointestinal perforation on tocilizumab were primarily reported as complications of diverticulitis including generalised purulent peritonitis, lower gastrointestinal perforation, fistulae and abscess.
Risk factors and risk groups	Patient with a previous history of intestinal ulceration or diverticulitis.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide
Important identified risk: Neutropenia	
Evidence for linking the risk to medicine	Neutropenia is a condition where the body does not have enough neutrophils, an important type of white blood cells. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 1500/µL. Severe neutropenia is defined as less than 500/µL (AAAAI). Neutropenia has been reported in the Clinical development programme of the reference product. There was a higher incidence of Grade 1 or 2 neutropenia among patients weighing less than < 60 kg compared with patients in higher body weight categories. In the IV RA population in the reference product clinical studies, 250 of the 4163 patients developed grade 3 or 4 neutropenia. In the COVID-19 clinical studies (WA42380, WA42380 and WA42511 studies), 6 cases of Grade 4 neutropenia were reported amongst 724 patients treated with tocilizumab. In the 6-month controlled trials with reference product decreases in neutrophil counts below 1 x 10^9/L occurred in 3.4% of patients on tocilizumab 8 mg/kg plus DMARDs compared to < 0.1% of patients on placebo plus DMARDs. Approximately half of the patients who developed an ANC < 1 x 10^9/L did so within

	8 weeks after starting therapy. Decreases below 0.5 x 10^9/L were reported in 0.3% patients receiving tocilizumab 8 mg/kg plus DMARDs Neutropenia associated with the use of tocilizumab in COVID-19 has been reported in scientific literature. 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).
Risk factors and risk groups	None identified.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4, and 4.8 PIL section 4 Legal status: Prescription only medicine <u>Additional risk minimisation measures:</u> Patient Brochure Healthcare Provider Brochure Dosing Guide
Important identified risk: Hepatotoxicity	
Evidence for linking the risk to medicine	Tocilizumab commonly causes mild serum liver enzyme elevations that are usually short lived and asymptomatic, but has also been linked to rare instances of clinically apparent liver injury with jaundice, and occasional reactivation of hepatitis B (LiverTox, 2021). In the clinical development programme of the reference product, mild and moderate elevations of liver enzymes have been observed with tocilizumab treatment. Increased frequency of these elevations was observed when drugs, which are known to cause liver toxicity (e.g., methotrexate), were used in combination with tocilizumab.
Risk factors and risk groups	Patient with 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., may impact individual background risk. Patients with COVID-19 frequently experience hepatic injury of various degrees (Saha et al., 2022). Treatment with other hepatotoxic drugs (e.g., MTX)

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 PIL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient Alert Card Patient Brochure Healthcare Provider Brochure
Important potential risk: Thrombocytopenia and the potential risk of bleeding	
Evidence for linking the risk to medicine	Thrombocytopenia is the condition characterised by a platelet count below the lower limit of normal for adults, i.e., 150 x 10^3/µL. Platelets are blood cells that help in blood clotting and wound healing risks associated with thrombocytopenia range from no risk at all to bleeding risks and thrombosis. The correlation between severity of thrombocytopenia and bleeding risk is uncertain. (Jinna et al., 2023). In the clinical studies with reference product, 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.
Risk factors and risk groups	Advanced patient age and a low platelet count prior to tocilizumab treatment were associated with the development of thrombocytopenia after treatment (Lee et al., 2019).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure
Important potential risk: Elavated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	
Evidence for linking the risk to medicine	Elevated levels of blood lipids are well documented risk factors for cardiovascular disease. The problem can be due solely to hereditary factors, but more commonly it is an acquired condition (Nelson, 2013). In the clinical studies with the reference product, increases in total cholesterol, low density lipoprotein (LDL), and triglyceride levels have been observed in patients following treatment with tocilizumab. The relationship of these elevations and the risk for cardiovascular/cerebrovascular disease is unknown.
Risk factors and risk groups	None identified.

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, and 4.8 PIL sections 2 and 4 Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide
Important potential risk: Malignancies	
Evidence for linking the risk to medicine	According to published scientific literature evidence, patients with rheumatoid arthritis (RA) are at similar risk for most types of malignancies compared with the general population; however, they are at increased risk for certain anatomical site-specific malignancies, such as lymphoma and lung cancer, and may even be at increased risk for skin cancer, particularly non-melanoma skin cancer (NMSC). Large epidemiological studies show that risk for lung malignancy is estimated to be 20-80% higher, risk for lymphoma is approximately twice as high and risk for NMSC is 60-90% higher in patients with RA compared with the general population. Some observational and clinical trial data failed to demonstrate an increased risk of malignancies (Rubbert-Roth et al., 2016). In the clinical studies with reference product, the rates and types of malignancies observed in the IV and SC tocilizumab populations were consistent over time. The incidence rates of malignancies in the IV RA and SC RA all exposure population were 1.26 (95% CI: 1.09, 1.44) and 1.24 events per 100 PY (95% CI: 0.76, 1.92) events per 100 PY, respectively.
Risk factors and risk groups	The risk for malignancy, including haematological malignancy, is potentially greater in patients with RA who use immunosuppressive agents (Rubbert-Roth et al., 2016).
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 Legal status: Prescription only medicine Additional risk minimisation measures: Patient Brochure Healthcare Provider Brochure Dosing Guide
Important potential risk: Demyelinating Disorders	
Evidence for linking the risk to medicine	The demyelinating diseases are common neurological disorders that affect the central nervous system (CNS) and peripheral nervous system. They cause substantial disability and some are associated with a high mortality rate if not treated promptly (Javed et al., 2009).

	In the clinical development programme of the reference product, there have been very few reports of nerve damage (demyelination) in patients treated with tocilizumab.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Legal status: Prescription only medicine Additional risk minimisation measures: Healthcare Provider Brochure
Important potential risk: Immunogenicity	
Evidence for linking the risk to medicine	Immunogenicity is caused when a drug is detected by the body's immune system as a foreign substance and the body then elicits an immune response to the drug. (Gunn et al, 2016). In the clinical studies of the reference product, positive anti-tocilizumab antibodies were detected using confirmation assay. In the IV RA all exposure population, a total of 44 of 3945 patients tested positive for anti-tocilizumab antibodies, 5 of whom also experienced a serious hypersensitivity reaction. Of the 1462 patients in the SC all exposure population who were tested for anti-tocilizumab antibodies, 20 (1.4%) patients developed anti-tocilizumab antibodies.
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 Legal status: Prescription only medicine Additional risk minimisation measures: None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

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 Avtozma.

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

There are no studies required for Avtozma.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

The targeted follow-up forms will be used for the follow up of cases for the following risks:

- Serious infections
- Complications of Diverticulitis
- Neutropenia
- Hepatotoxicity
- Thrombocytopenia and the potential risk of bleeding
- Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events
- Malignancies
- Demyelinating Disorders

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Spontaneous or Serious/Non Serious Bleeding Event (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Demyelination Events (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab) – Gastrointestinal Perforation and Related Events (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Medically Significant Hepatic Event (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Infections (Including Opportunistic Infections (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Myocardial Infarction/Acute Coronary Syndrome (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Malignancy (Version 1.0)

Targeted Follow-up Checklist for Avtozma (Tocilizumab)- Stroke (Version 1.0)

Tocilizumab Guided Questionnaire
Spontaneous or Serious/Non Serious Bleeding Event

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

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

Reported Term

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

☐ **Medically Significant** (important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes) ☐ **Non-Serious**	
Related to Tocilizumab?	☐ Yes ☐ No
Outcome of the event:	☐ Persisting ☐ Improved ☐ Recovered with sequalae ☐ Death ☐ Resolved ☐ Unknown ☐ Worsened
Was the bleeding event associated with a platelet count of <100,000/mm^3?	☐ No ☐ Yes: Provide Date of abnormal labs (MM/DD/YYYY): ☐ Unknown
Did dose modification occur in association with lab abnormality?	☐ No ☐ Yes: Provide Date of dose modification (MM/DD/YYYY): ☐ Unknown

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

Treatment for the event
What treatment was initiated for the event? (including any pre-hospitalization treatment)

Endoscopic Treatment		
Surgery		
Treatment	**Dosing Regimen**	**Dates of Therapy (MM/DD/YYYY to MM/DD/YYYY)**

Please attach all laboratory results (haemoglobin, hematocrit, platelet count, etc) and imaging tests. Please provide SI (International System of Units) if available. Otherwise, as reported.
☐Labs Attached

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

	Baseline Value (Prior to TCZ Use)	**Date of Baseline Test (MM/DD/YYYY)**	**Date of Test (MM/DD/YYYY)**	**Test Results (include units)**	**Reference Range (If Applicable)**	**Pending?**
Fecal Occult Blood Test						☐Yes
Urinalysis						☐Yes
INR						☐Yes
CT Scan						☐Yes
MRI						☐Yes
Colonoscopy						☐Yes
Endoscopy						☐Yes
Other Please specify:						☐Yes

Risk Factors

Please indicate if the following conditions are either part of the patient's medical history or *are still active conditions.*

Haemophilia	☐History	☐Concurrent	☐Not present
Von Willebrand's disease	☐History	☐Concurrent	☐Not present
Previous Event of Haemorrhage Specify:	☐History	☐Concurrent	☐Not present
Other, please specify:	☐History	☐Concurrent	☐Not present

Past/Concomitant Medications
☐Medication List Attached

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

Corticosteroids Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Aspirin/ anti-platelet Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
NSAIDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Coumarin/Coumadin	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Heparin	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
SSRIs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Ginkgo Biloba	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Other Please specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Demyelination Events

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

Demyelination events have been observed in some patients treated with Tocilizumab.

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

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

Reported Term

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

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

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

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

Laboratory tests/ Imaging

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

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

	Baseline Value (Prior to TCZ Use)	**Date of Baseline Test (MM/DD/YYYY)**	**Date of Test (MM/DD/YYYY)**	**Test Results (include units)**	**Reference Range (If Applicable)**	**Pending?**

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

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Immunodeficiency Specify:	☐History	☐Concurrent	☐Not present
Viral infection Specify:	☐History	☐Concurrent	☐Not present
JC Virus	☐History	☐Concurrent	☐Not present
Lyme Disease	☐History	☐Concurrent	☐Not present
Other opportunistic infections Specify:	☐History	☐Concurrent	☐Not present
Other infections Specify:	☐History	☐Concurrent	☐Not present
SLE	☐History	☐Concurrent	☐Not present
Collagen vascular disease	☐History	☐Concurrent	☐Not present

Complications from previous immunosuppressive medication/conditions Specify:	☐History	☐Concurrent	☐Not present
Diabetes mellitus	☐History	☐Concurrent	☐Not present
Arteriosclerosis Specify:	☐History	☐Concurrent	☐Not present
Multiple Sclerosis	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

Past/Concomitant Medications
☐Medication List Attached

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

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Gastrointestinal Perforation and Related Events

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

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

Reported Term

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

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

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

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

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Gastric ulcers Specify:	☐History	☐Concurrent	☐Not present
Duodenal ulcers Specify:	☐History	☐Concurrent	☐Not present

Inflammatory bowel disease Specify:	☐History	☐Concurrent	☐Not present
Diverticulosis Specify:	☐History	☐Concurrent	☐Not present
Diverticulitis Specify:	☐History	☐Concurrent	☐Not present
Gastrointestinal obstruction Specify:	☐History	☐Concurrent	☐Not present
Abdominal pain	☐History	☐Concurrent	☐Not present
Abdominal abscess	☐History	☐Concurrent	☐Not present
Fistula	☐History	☐Concurrent	☐Not present
Gastrointestinal bleeding Specify:	☐History	☐Concurrent	☐Not present
Cancer Specify:	☐History	☐Concurrent	☐Not present
Smoking	☐History	☐Concurrent	☐Not present
Alcohol abuse	☐History	☐Concurrent	☐Not present
Abdominal Surgery Specify:	☐History	☐Concurrent	☐Not present
Colonoscopy	☐History	☐Concurrent	☐Not present
Endoscopy	☐History	☐Concurrent	☐Not present
Other Please Specify:	☐History	☐Concurrent	☐Not present

Laboratory tests/ Imaging

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

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

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

Past/Concomitant Medications

☐**Medication List Attached**

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

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Medically Significant Hepatic Event

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

Reported Term

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

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

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

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

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Pre-existing hepatobiliary Disorder Specify	☐History	☐Concurrent	☐Not present
Pancreatic Disorder Specify:	☐History	☐Concurrent	☐Not present
Drug Allergy Specify:	☐History	☐Concurrent	☐Not present
Previous Drug Reactions Specify:	☐History	☐Concurrent	☐Not present
Auto-Immune Disease Specify:	☐History	☐Concurrent	☐Not present
Surgical Procedures Specify:	☐History	☐Concurrent	☐Not present
Blood Transfusion Specify:	☐History	☐Concurrent	☐Not present
Alcohol use Specify:	☐History	☐Concurrent	☐Not present
Tattoo Specify:	☐History	☐Concurrent	☐Not present
Acupuncture Specify:	☐History	☐Concurrent	☐Not present
IV Drug Abuse Specify:	☐History	☐Concurrent	☐Not present
Sexually Transmitted Diseases Specify:	☐History	☐Concurrent	☐Not present
Diabetes Mellitus Specify:	☐History	☐Concurrent	☐Not present
Obesity Specify:	☐History	☐Concurrent	☐Not present
Non-alcoholic steatohepatitis Specify	☐History	☐Concurrent	☐Not present
Viral hepatitis Specify:	☐History	☐Concurrent	☐Not present
Family History of Liver Disease Specify:	☐History	☐Concurrent	☐Not present
Recent Travel to Endemic areas for viral hepatitis Specify:	☐History	☐Concurrent	☐Not present
CHF	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

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

☐Labs Attached

Please indicate if any of the following tests have been performed, and the result:						
	Baseline Value (Prior to TCZ Use)	**Date of Baseline Test (MM/DD/YYYY)**	**Date of Test (MM/DD/YYYY)**	**Test Results (include units)**	**Reference Range (If Applicable)**	**Pending?**
ANA						☐Yes
Liver biopsy• Please obtain biopsy report if available						☐Yes
CT Scan						☐Yes
MRI						☐Yes
Ultrasound						☐Yes
Other Please specify:						☐Yes

Serology Results			
Please indicate if any of the following tests have been pet1ormed, and the result			
Test	**Conducted?**	**Results**	**Date (MM/DD/YYYY)**
Hepatitis A	☐Yes ☐No		
Hepatitis B	☐Yes ☐No		
Hepatitis C	☐Yes ☐No		
Hepatitis D	☐Yes ☐No		
Anti-CMV	☐Yes ☐No		
Anti-EBV	☐Yes ☐No		
Anti-Nuclear Ab	☐Yes ☐No		
Anti-mitochondrial Ab	☐Yes ☐No		
Other: Please specify:	☐Yes ☐No		

Past/Concomitant Medications

☐Medication List Attached

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

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Infections (Including Opportunistic Infections)

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

Reported Term

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

Was the patient neutropenic at the current time of the serious or opportunistic infectious event?	☐No ☐Yes: Provide lab results including Date of abnormal labs if available (MM/DD/YYYY): ☐Unknown
Was the infection associated with an ANC of <1000/mm^3 (1.0 x 10^9/L)?	☐No ☐Yes: Provide Date of abnormal labs (MM/DD/YYYY): ☐Unknown
Did dose modification occur in association with lab abnormality?	☐No ☐Yes: Provide Date of dose modification (MM/DD/YYYY): ☐Unknown

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

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

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

☐**Labs Attached**

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

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

Risk Factors

Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.

Diabetes Mellitus	☐History	☐Concurrent	☐Not present
HIV Infection	☐History	☐Concurrent	☐Not present
Felty's syndrome: long standing RA, splenomegaly, and low WBC Specify:	☐History	☐Concurrent	☐Not present
Splenectomy	☐History	☐Concurrent	☐Not present
Indwelling catheter	☐History	☐Concurrent	☐Not present
Previous Infection? Specify:	☐History	☐Concurrent	☐Not present
Recent Travel? Specify:	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

Has the patient ever received TB prophylaxis or active treatment? If yes, provide details below.

Product Name	Prophylactic or Active Treatment?	Dose	Date started	Date stopped

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

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

In the few weeks following the infection, what was the specific Immunoglobulin titer to the infectious agent (if available):

lgG	Date (MM/DD/YYYY)	Result:
lgM	Date (MM/DD/YYYY)	Result:
lgA	Date (MM/DD/YYYY)	Result:
Other tests: Please specify:	Date (MM/DD/YYYY)	Result:

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Myocardial Infarction/Acute Coronary Syndrome

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

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

Reported Term

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

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

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

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

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

☐Labs Attached

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

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

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Family history of cardiovascular disease Specify:	☐History	☐Concurrent	☐Not present
Coronary Artery Disease Specify:	☐History	☐Concurrent	☐Not present
Previous Myocardial infarction	☐History	☐Concurrent	☐Not present
Cardiac Valve Disease	☐History	☐Concurrent	☐Not present
Diabetes Mellitus	☐History	☐Concurrent	☐Not present
Hypertension	☐History	☐Concurrent	☐Not present
Hypercholesterolemia	☐History	☐Concurrent	☐Not present
Smoking	☐History	☐Concurrent	☐Not present
Obesity	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

Past/Concomitant Medications

☐Medication List Attached

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

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

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Malignancy

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

Reported Term

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

Description of the event			
Event led to	1. surgery	☐ Yes	☐ No
	2. radiotherapy	☐ Yes	☐ No
	3. chemotherapy	☐ Yes	☐ No
Hospital Admission ☐ Yes (Admission Date MM/DD/YYYY): (Discharge Date MM/DD/YYYY):			☐ No
Onset Date (MM/DD/YYYY)			
Stop Date (MM/DD/YYYY)			
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (MM/DD/YYYY) ☐**Life-Threatening** (use only if patient was at immediate risk of death due to event)			

☐ **Initial/Prolonged Hospitalization** ☐ **Congenital Anomaly/Birth Defect** ☐ **Persistent or Significant Disability** ☐ **Medically Significant** (important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes) ☐ **Non-Serious**	
Related to Tocilizumab?	☐ Yes ☐ No
Outcome of the event:	☐ Persisting ☐ Improved ☐ Recovered with sequalae ☐ Death ☐ Resolved ☐ Unknown ☐ Worsened

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

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

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

Past/Concomitant Medications

☐ **Medication List Attached**

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

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

☐Labs Attached

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Tocilizumab Guided Questionnaire
Stroke

AER:		Local Case ID:	
Site No:		Patient Date of Birth (MM/DD/YYYY):	
Patient ID/Initials:		Patient Gender:	☐M ☐F
Patient Weight	☐ kg ☐ lb	Patient Height	☐cm ☐ inch

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

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

Reported Term

Description of the event		
Type of Stroke:	☐Ischemic: ☐Hemorrhagic ☐Other/unknown-please specify	
Hospital Admission	☐Yes (Admission Date MM/DD/YYYY): (Discharge Date MM/DD/YYYY):	☐No
Onset Date (MM/DD/YYYY)		
Stop Date (MM/DD/YYYY)		

Select all that apply:

SERIOUSNESS CRITERIA CLASSIFICATION

☐**Death** Date of Death (MM/DD/YYYY)

☐**Life-Threatening** (use only if patient was at immediate risk of death due to event)

☐**Initial/Prolonged Hospitalization**

☐**Congenital Anomaly/Birth Defect**

☐**Persistent or Significant Disability**

☐**Medically Significant** (important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes)

☐**Non-Serious**

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

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

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

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

☐ **Labs Attached**

Please indicate if any of the following tests have been performed, and the result:						
	Baseline Value (Prior to TCZ Use)	**Date of Baseline Test (MM/DD/YYYY)**	**Date of Test (MM/DD/YYYY)**	**Test Results (include units)**	**Reference Range (If Applicable)**	**Pending?**
CT Scan						☐Yes
MRI						☐Yes
Carotid Doppler						☐Yes
MRA (Magnetic Resonance Angiogram)						☐Yes
Cerebral Arteriogram						☐Yes
Other Please specify:						☐Yes

Risk Factors *Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.*			
Prior Stroke Specify:	☐History	☐Concurrent	☐Not present
Prior TIA Specify:	☐History	☐Concurrent	☐Not present
Prior Heart Attack Specify:	☐History	☐Concurrent	☐Not present
Hypertension	☐History	☐Concurrent	☐Not present
Smoking Specify:	☐History	☐Concurrent	☐Not present
Diabetes Mellitus	☐History	☐Concurrent	☐Not present
Coronary artery Disease Specify:	☐History	☐Concurrent	☐Not present
Atrial Fibrillation	☐History	☐Concurrent	☐Not present
Sickle Cell Anemia	☐History	☐Concurrent	☐Not present
Hypercholesterolemia	☐History	☐Concurrent	☐Not present
Physical Inactivity	☐History	☐Concurrent	☐Not present
Obesity	☐History	☐Concurrent	☐Not present
Low platelet count	☐History	☐Concurrent	☐Not present
Cardiac valvular disease	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

Past/Concomitant Medications

☐**Medication List Attached**

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

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

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

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

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

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

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

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
  - The product must not be given to patients with active or suspected infection
  - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Risk of Hepatotoxicity
  - Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x ULN treatment is not recommended.
  - In RA, GCA, pJIA and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC section 4.2.
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients
- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

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

The Patient Information Pack should contain the following key elements:

- Package leaflet covering all approved indications (with instructions for use for SC formulation)
- Patient alert card
  - To address the risk of getting infections which can become serious if not treated. In addition,

some previous infections may reappear.
– To address the risk that patients using Avtozma may develop complications of diverticulitis which can become serious if not treated.
– To address the risk that patients using Avtozma may develop serious hepatic injury. Patients would be monitored for liver function tests. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, abdominal pain and jaundice