PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for SIMPONI (golimumab)

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

SIMPONI's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how SIMPONI should be used.

This summary of the RMP for SIMPONI 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 SIMPONI's RMP.

I. The Medicine and What it is Used For

SIMPONI is authorized for rheumatoid arthritis (RA), psoriatic arthritis (PsA), nonradiographic axial spondyloarthritis (nr-AxSpA), ankylosing spondylitis (AS), ulcerative colitis (UC), and polyarticular juvenile idiopathic arthritis (JIA) (pJIA) (see SmPC for the full indication). It contains golimumab as the active substance and it is given by subcutaneous (SC) injection using a prefilled syringe, prefilled pen, and pediatric prefilled pen.

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

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of SIMPONI, together with measures to minimize such risks and the proposed studies for learning more about SIMPONI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can include:

- Specific information, such as warnings, precautions, and advice on correct use included in the PL addressed to patients and the SmPC addressed to HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size, ie, the amount of medicine in a single pack which is chosen to ensure that the medicine is used correctly;
- The medicine's legal status, ie, the way a medicine is supplied to the patient (eg, with or without prescription).

Together, these measures constitute routine risk minimization measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Benefit Risk Evaluation Reports/Periodic Safety Update Reports assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance (PV) activities.

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

II.A. List of Important Risks and Missing Information

Important risks of SIMPONI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SIMPONI. 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 (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	Serious infections Demyelinating disorders Malignancy
Important potential risks	Serious depression including suicidality Colon cancer/dysplasia (in ulcerative colitis) Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero*
Missing information	Long-term safety in adult patients with UC Long-term safety in pediatric patients Exposure during pregnancy

II.B. Summary of Important Risks

Important Identified Risk: Serious infections	
Evidence for linking the risk to the medicine	Because they suppress the immune system, drugs that inhibit tumor necrosis factor alpha (TNFα) have been associated with an increased risk of serious infections (some fatal), including opportunistic infections, tuberculosis (TB), and invasive fungal infections. Drugs that inhibit TNFα have also been associated with hepatitis B virus (HBV) reactivation in patients who are chronic carriers of the virus. Serious infections, including opportunistic infections and TB, have been reported in patients treated with SIMPONI in clinical trials and in the postmarketing setting. Hepatitis B virus reactivation has been reported in the postmarketing setting in patients treated with SIMPONI. These findings are consistent with nonclinical data and published medical literature. Serious infections is considered an important identified risk because of the consistency of evidence across multiple sources, including data from products in the same class.
Risk factors and risk groups	<u>Serious Infections</u> Risk factors for the development of serious infections include the use of steroids, other immunosuppressive drugs (including methotrexate [MTX]), or other biologics at the same time as SIMPONI. <u>Opportunistic Infections</u> People whose immune status is compromised are susceptible to opportunistic infections. Risk factors for opportunistic infections may therefore include human immunodeficiency virus (HIV) disease, increased age, having an organ transplant, immunosuppressive drug therapy (corticosteroids, MTX, azathioprine, and biologic agents), chronic pulmonary disease, and chronic renal failure. <u>Invasive Fungal Infections</u> People who have resided in or travelled to regions where invasive fungal infections are common are at increased risk. <u>Tuberculosis</u> The most common risk factors for the development of TB include conditions that weaken the immune system such as advanced age, HIV infection, alcohol abuse, malignancy, corticosteroids or other

Important Identified Risk: Serious infections	
	immunosuppressive drugs such as MTX, connective tissue disease, renal failure, diabetes, and pregnancy. Other risk factors for the development of TB include contact with a person with active TB infection and having been born in, lived in, or travelled to countries where the incidence of TB is high. Exposure to TB may occur through various health care settings (eg, hospitals and nursing homes) or high-density institutions (eg, prisons). <u>Hepatitis B Virus Reactivation</u> Risk factors for the acquisition of HBV include being born to a mother from a highly endemic area, emigration from a highly endemic area, history of intravenous drug use, and a history of multiple sexual partners. Patients at risk for HBV reactivation are those who are chronic carriers of this virus (ie, surface antigen-positive), especially those who become immunosuppressed. Approximately 14% to 50% of immunosuppressed patients who are chronic carriers of HBV will experience acute reactivations during the natural history of their disease. Thus, risk factors for HBV reactivation in patients with a history of HBV infection include the concomitant use of medications that suppress the immune system (eg, chemotherapy, corticosteroids, MTX, azathioprine, TNFα inhibitors). Other risk factors that may contribute to HBV reactivation include HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive therapies.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.3 (Contraindications)* • *SmPC Section 4.4 (Special Warnings and Precautions for Use)* • *SmPC Section 4.8 (Undesirable Effects) and PL Section 4* Additional risk minimization measures: • *Patient Reminder Card*
Additional PV activities	Additional PV activities: • *P04480* • *MK-8259-050* See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Demyelinating disorders	
Evidence for linking the risk to the medicine	Demyelinating disorders (both central and peripheral) have been associated with the use of TNFα inhibitors. SIMPONI has been investigated in multiple settings. Demyelinating disorders have been reported in clinical trials and in the postmarketing setting in patients treated with SIMPONI. Demyelinating disorders are considered an important identified risk because of the consistency of evidence across multiple sources, including data from products in the same class.
Risk factors and risk groups	Multiple sclerosis (MS) and other autoimmune diseases have been linked to genetic and environmental factors. First-degree relatives of MS patients are at greater risk of developing MS than the general population. Whites, particularly of northern European descent, are also more likely to develop MS. Several studies have suggested an association between smoking and MS. Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.4 (Special Warnings and Precautions for Use)* • *SmPC Section 4.8 (Undesirable Effects) and PL Section 4* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *P04480* • *MK-8259-050* See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Malignancy	
Evidence for linking the risk to the medicine	Reports of malignancies in golimumab-treated subjects, including lymphoma, skin cancer, and leukemia, have been received in clinical trials and in the postmarketing setting. For non-lymphoma malignancies (excluding nonmelanoma skin cancer [NMSC]), the incidence was similar between the golimumab and the control groups in the controlled portions of the golimumab pivotal trials and through approximately 4 years of

Important Identified Risk: Malignancy	
	follow-up. The incidence was also similar to the incidence in the general population. For lymphoma, more cases have been observed among patients receiving anti-TNFα treatment compared with control patients in the controlled portions of clinical trials of all TNFα-blocking agents, including golimumab. However, there is an increased background risk for lymphoma in RA patients with long standing, highly active, inflammatory disease, which complicates risk estimation. During the golimumab Phase 2b and 3 SC clinical trials in RA, PsA, and AS, the incidence of lymphoma in golimumab-treated subjects was higher than expected compared to the general population. In the controlled and uncontrolled portions of these trials with a median follow up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Looking specifically at children, adolescents, and young adults (up to 22 years of age), postmarketing cases of malignancies, some fatal, have been reported in patients who received TNFα inhibitors (initiation of therapy ≤18 years of age) to treat JIA, Crohn's disease, or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as MTX, azathioprine, or 6-mercaptopurine. It is not clear whether children with certain autoimmune conditions have an increased risk for malignancy given limited data. For hepatosplenic T-cell lymphoma (HSTCL), there have been rare reports in the postmarketing setting in patients treated with other TNFα inhibitors. The development of malignancy is considered an important identified risk because the effects attributed to TNFα in published medical literature, suggesting that certain types of malignancies may be adversely affected by TNFα blockade, may apply to SIMPONI.
Risk factors and risk groups	Because disease severity, cumulative disease activity, and disease duration may also contribute to an increased risk of malignancy in patients with immune-mediated diseases, it is difficult to distinguish the individual contribution of immunosuppressive medications, including those like SIMPONI that inhibit TNFα, from other risk factors for the development of malignancy. This is further complicated by the fact that patients with severe disease are

Important Identified Risk: Malignancy	
	more likely to have been treated with one or more immunosuppressive medications. There are a number of conflicting studies related to the risk of malignancies with the use of MTX. A retrospective analysis of 16,263 RA patients registered at the Mayo Clinic between 1976 and 1992 showed no relationship between the development of malignancy and the dose or duration of MTX compared with any other disease-modifying anti-rheumatic drug. Information regarding additional risk factors for the malignancy subtypes included in the broad category of malignancy is given below. <u>Lymphoma</u> • Lymphoma: Risk factors for the development of lymphoma include older age, male gender, family history, immunosuppression (due to medications [such as immunosuppression for organ transplants, chemotherapy for cancer or treatment for autoimmune diseases], infection with HIV, or from immune deficiencies due to an inherited syndrome), autoimmune diseases with chronic inflammation (RA, systemic lupus erythematosus, Sjogren syndrome, celiac disease), infections that directly transform lymphocytes (human T-cell lymphotropic virus, Epstein-Barr virus, human herpes virus 8), infections that cause chronic immune stimulation (*Helicobacter pylori*, C*hlamydophila psittaci*, *Campylobacter jejuni*, chronic hepatitis C infection), radiation exposure, and exposure to certain chemicals among others. • Hepatosplenic T-cell lymphoma: young men, the immunocompromised, and patients undergoing solid organ transplantation appear to be at a higher risk for HSTCL. <u>Skin Cancer</u> • Melanoma: Risk factors for the development of melanomas can be categorized as environmental or host factors. Exposure to ultraviolet (UV) light, especially in patients with a fair complexion, history of sunburns, and poor ability to tan, is the most strongly correlated environmental risk factor with the development of melanoma. Patients with xeroderma pigmentosum who do not have the ability to repair UV light-induced deoxyribonucleic acid damage are particularly susceptible. Family or personal history of melanoma and/or certain gene mutations are strong host risk factors. Additional host risk factors include the presence of 5 or more dysplastic nevi, a large number of nevi, and giant congenital nevus. Patients with conditions that are associated with immune

Important Identified Risk: Malignancy	
	suppression (ie, HIV, organ transplantation) are at higher risk of developing melanomas. • Nonmelanoma skin cancer: The risk factors for squamous cell carcinoma (SCC) include chronic UV light exposure (UVA and UVB), increasing age, arsenic exposure, genetic predisposition, therapeutic radiation exposure, and immunosuppression. The risk factors for basal cell carcinoma include all those for SCC in addition to basal cell nervous syndrome. With respect to patients with RA, epidemiological trials have generally shown that skin cancers are increased in this group, and immunosuppression may potentiate this risk by shortening the time taken to develop a malignancy. With respect to psoriasis patients, a higher risk of NMSC is seen in those with prior coal tar, UVB therapy, psoralen plus UVA light therapy, retinoids, and cyclosporine therapy. • Merkel cell carcinoma (MCC): Although the cause of MCC remains unclear, risk factors associated with its development include exposure to UV radiation, immunosuppression, and possibly viral causes. Most MCCs are located on sun exposed areas, particularly the head and neck, extremities, and trunk. Merkel cell carcinoma occurs most frequently in elderly white patients and affects males more commonly than females. Immunosuppression increases the risk of MCC in patients with HIV and in solid-organ transplant patients. Patients with other tumors, such as SCC and chronic lymphocytic leukemia, also have an increased risk of MCC. <u>Leukemia</u> Risk factors for the development of leukemia include genetic abnormalities, family history, radiation exposure, chemotherapy, autoimmune diseases with chronic inflammation and exposure to certain chemicals among others.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.4 (Special Warnings and Precautions for Use)* • *SmPC Section 4.8 (Undesirable Effects) and PL Section 4* Additional risk minimization measures: • *None*

Important Identified Risk: Malignancy	
Additional PV activities	Additional PV activities: • *P04480* • *MK-8259-013 (HSTCL only)* • *MK-8259-042 (HSTCL only)* • *MK-8259-050* See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Serious depression including suicidality	
Evidence for linking the risk to the medicine	SIMPONI has been investigated in multiple settings. In clinical trials, serious depression including suicidality has been reported in patients treated with SIMPONI. Depression has also been reported in the postmarketing setting and is described in published medical literature. Although serious depression has been reported in patients treated with SIMPONI, a causal association between the development or worsening of serious depression (including suicidality) and SIMPONI has not been established. Complicating the assessment is evidence that patients with RA, AS, and PsA have increased rates of depression compared to the general population. Additionally, while some researchers have found no evidence of an association between depression and UC, others have suggested that depression and anxiety are common in patients with inflammatory bowel disease.
Risk factors and risk groups	Risk factors for depression include older age and associated neurologic conditions, recent childbirth, stressful life events, a personal or family history of depression, and selected medical comorbid conditions. Suicide rates are twice as high in families of suicide victims.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.8 (Undesirable Effects) and PL Section 4* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *MK-8259-050* See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Colon cancer/dysplasia (in ulcerative colitis)	
Evidence for linking the risk to the medicine	Colorectal cancer (CRC) is a complication of chronic UC. The cumulative probability of developing this malignancy in chronic UC is significantly higher than in the general population, making chronic UC the third highest risk condition for CRC. Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF inhibitors, including SIMPONI, to cause immunosuppression affecting host defenses against malignancies. However, as TNF inhibitors are associated with mucosal healing in patients with active UC, it is also possible that they decrease the risk of colon cancer/dysplasia. In UC clinical trials, colon cancer/dysplasia has been reported in golimumab-treated subjects. Colon cancer/dysplasia (in ulcerative colitis) was therefore considered an important potential risk for SIMPONI.
Risk factors and risk groups	Patients with long-standing UC or primary sclerosing cholangitis, or who had a prior history of dysplasia or colon cancer are at a higher risk for developing colon cancer or dysplasia. Other risk factors for development of colorectal dysplasia and cancer in patients with UC include extent of disease, family history of CRC, young age at diagnosis, and the presence of a condition known as backwash ileitis (ileal inflammation in the context of UC).
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *MK-8259-013* • *MK-8259-042* See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Breakthrough infection after administration of live vaccines in infants exposed to golimumab *in utero*	
Evidence for linking the risk to the medicine	A small number of cases of breakthrough infection have occurred after administration of live vaccines in infants exposed to another TNFα-blocking agent *in utero*. A cumulative search of the postmarketing safety database from launch through 06 April 2018 did not identify any cases of breakthrough infections following administration of live (attenuated) vaccines in infants born to women who received SIMPONI. Additionally, no cases have been identified in SIMPONI clinical trials.
Risk factors and risk groups	Infants exposed to SIMPONI in utero and who receive live (attenuated) vaccines within 6 months after birth may be at risk for developing breakthrough infection.
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.4 (Special Warnings and Precautions for Use)* • *SmPC Section 4.6 (Fertility, Pregnancy, and Lactation)* • *PL Section 2* Additional risk minimization measures: • *Patient Reminder Card*
Additional PV activities	Additional PV activities: • *None*

Missing information: Long-term safety in adult patients with UC	
Risk minimization measures	Routine risk minimization measures: • *None* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *MK-8259-013* • *MK-8259-042* See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Long-term safety in pediatric patients	
Risk minimization measures	Routine risk minimization measures: • *None* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *CNTO148UCO1001* • *MK-8259-050* See Section II.C of this summary for an overview of the postauthorization development plan.

Missing information: Exposure during Pregnancy	
Risk minimization measures	Routine risk minimization measures: • *SmPC Section 4.6 (Fertility, Pregnancy, and Lactation)* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *CNTO148ART4001* • *MK-8259-050* See Section II.C of this summary for an overview of the postauthorization development plan

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of SIMPONI.

II.C.2. Other Studies in Postauthorization Development Plan

Study	Purpose of the Study
P04480: Long-term observation of treatment with biologics in rheumatoid arthritis	To evaluate the long-term safety of biologics. A minimum follow-up period of 5 years is planned in golimumab. To address the safety concerns of: • Serious infections • Demyelinating disorders • Malignancy

Study	Purpose of the Study
CNTO148ART4001: Exposure to golimumab during pregnancy: A review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers	To use the Swedish, Danish, and Finnish medical birth registers to collect and analyze information pertaining to pregnancy outcomes of women exposed to golimumab during pregnancy and the health status during the first year following delivery of their infants, relative to the background risk in patients treated with other biologics, non-biologic systemic therapy, and general population controls. To collect and analyze information pertaining to health status, during the first year following delivery, of infants born to women following prenatal exposure to golimumab, infants born to women with diseases of interest but treated with other biologics, infants born to women with diseases of interest but treated with non-biologic systemic therapy, and infants born to general population controls. To address the safety concern of exposure during pregnancy.
MK-8259-013: A non-interventional observational longitudinal postauthorization safety study (PASS) of SIMPONI in treatment of ulcerative colitis using Nordic National Health Registries	To describe the risk of the following endpoints in patients exposed to golimumab and alternative therapies: • Incident CRC • All-cause total colectomy • Incident HSTCL To address the safety concerns of: • Colon cancer/dysplasia (in ulcerative colitis) • Malignancy (HSTCL only) • Long-term safety in adult patients with UC
CNTO148UCO1001: A Phase 1b open label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFα antibody, in pediatric subjects with moderately to severely active ulcerative colitis	To evaluate the pharmacokinetics and safety of golimumab in pediatric subjects aged 2 through 17 years with moderately to severely active UC; Additionally, to evaluate the efficacy of golimumab induction (ie, short-term therapy) in these pediatric subjects To address the safety concern of long-term safety in pediatric patients

Study	Purpose of the Study
MK-8259-050: An observational post-approval safety study of golimumab in treatment of polyarticular Juvenile Idiopathic Arthritis (pJIA) using the German Biologics JIA Registry (BiKeR)	An observational PASS to investigate long-term safety of golimumab in pJIA. To address the safety concerns of: • Serious infections • Malignancies • Exposure during pregnancy • Long-term safety in pediatric patients Secondary objectives will include crude incidence rates of • Demyelinating disorders • Serious depression including suicidality
MK-8259-042: A postauthorization safety study of golimumab in UC using the Spanish ENEIDA Registry	To describe the clinical and demographic profile of first-time users of golimumab in the treatment of UC compared with the corresponding profile of first-time users of comparator therapies (other anti-TNFα agents or thiopurines) For patients with UC initiating golimumab or other anti-TNFα agents, describe the risk of incident colectomy for intractable disease. For patients with UC initiating golimumab, other anti-TNF agent, or a thiopurine describe the risk of the composite endpoint of incident CRC or high-grade colorectal dysplasia (hereafter 'advanced colonic neoplasia'). To address the safety concerns of: • Colon cancer/dysplasia (in ulcerative colitis) • Malignancy (HSTCL only) • Long-term safety in adult patients with UC