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 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, psoriatic arthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, ulcerative colitis, and polyarticular juvenile idiopathic arthritis (see SmPC for the full indications). 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 EMA website, under the medicine's webpage:

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 package leaflet addressed to patients and the SmPC addressed to healthcare professionals;
- 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 Safety Update Report (PSUR) 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 including opportunistic infections and tuberculosis (TB) Demyelinating disorders Hypertension Lymphoma (excluding hepatosplenic T-cell lymphoma) Hepatitis B virus reactivation Congestive heart failure (CHF) Autoimmune processes Hematologic reactions Serious systemic hypersensitivity (including anaphylactic reaction) Skin cancer Leukemia
Important potential risks	Malignancy Serious hepatotoxicity Exposure during pregnancy

	Serum sickness Maladministration/administration error Serious depression including suicidality Colon cancer/dysplasia (in ulcerative colitis) Hepatosplenic T-cell lymphoma Medication error (wrong dose related to different strengths)
Missing information	Use in pediatric patients with ulcerative colitis Use in patients with hepatic impairment Use in patients with renal impairment Use in patients with a past history of latent or active TB Use in patients with concurrent malignancy or a history of malignancy Use in patients with active infections including HIV, hepatitis B, hepatitis C Use in patients with recent prior use of other biologics excluding anti-tumor necrosis factor alpha (TNFα) agents Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF Use in patients with history of demyelinating disease Use in patients with a history of lupus or lupus-like syndrome Use in patients after recent vaccination with live bacterial or viral vaccine Long-term safety in adult patients Long-term safety in pediatric patients

II.B. Summary of Important Risks

Important Identified Risk: Serious infections including opportunistic infections and tuberculosis	
Evidence for linking the risk to the medicine	Because they suppress the immune system, drugs that inhibit TNFα have been associated with an increased risk of serious infections (some fatal), including opportunistic infections, TB, and invasive fungal infections. Serious infections are considered a class effect of anti-TNFα agents. SIMPONI has been investigated in multiple settings. In clinical trials, serious infections, including opportunistic infections and TB, have been reported in patients treated with SIMPONI. This is consistent with nonclinical and postmarketing experience and published literature. Serious infection, including opportunistic infections and TB, 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	Serious Infections Risk factors for the development of serious infections include the use of steroids, other immunosuppressive drugs (including methotrexate), or other biologics at the same time as SIMPONI. Opportunistic Infections People whose immune status is compromised are susceptible to opportunistic infections. Risk factors for opportunistic infections may therefore include HIV disease, increased age, having an organ transplant, immunosuppressive drug therapy (corticosteroids, methotrexate, azathioprine, and biologic agents), chronic pulmonary disease, and chronic renal failure. Invasive Fungal Infections People who have resided in or travelled to regions where invasive fungal infections are common are at increased risk. Tuberculosis 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 immunosuppressive drugs such as methotrexate, 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).

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* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization 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 and are considered a class effect of these agents. 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 20-40 times more likely to develop MS than the general population. People with ancestors from northerly latitudes, particularly those of Celtic and Scandinavian descent, are also more likely to develop MS. Several studies have suggested an association between smoking and MS. Another possible risk factor for MS is month of birth. A large population-based trial found that the risk of MS is increased for those born in May and decreased for those born in November, suggesting that the gestational or neonatal environment influences the risk of MS later in life.

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 pharmacovigilance activities	Additional pharmacovigilance activities: • *P04480* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Hypertension	
Evidence for linking the risk to the medicine	Drugs that inhibit TNFα have been associated with an increased risk of hypertension. SIMPONI has been investigated in multiple settings. In clinical trials, hypertension has been reported in patients treated with SIMPONI. This is consistent with postmarketing reports, published medical literature, and experience with other medicines that also act by inhibiting TNF. Analysis of reported cases of hypertension in the SIMPONI program have shown both new onset hypertension, including in some cases a need for antihypertensive therapy, as well as worsening of pre-existing hypertension. Hypertension 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	Risk factors for development of hypertension include: age, Black race, diabetes mellitus, family history of hypertension, obesity, reduced physical activity, poor diet (excess sodium, reduced intake of fruits, vegetables, and potassium), and alcohol consumption.
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimization measures: • *None.*

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002 (new onset hypertension only)* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Lymphoma (excluding hepatosplenic T cell lymphoma [HSTCL])	
Evidence for linking the risk to the medicine	Drugs that inhibit TNFα have been associated with an increased risk of lymphoma and lymphoma is considered a class effect of these agents. SIMPONI has been investigated in multiple settings. Across the clinical trials program, the incidence of lymphoma was higher in the golimumab-treated subjects than in the placebo group. Reports of lymphoma have also been received from the postmarketing setting. The literature provides documentation that there is an association of increased risk for malignancy for patients treated with immunosuppressive drug therapy, commonly used in the treatment of RA. However, the potential role of disease severity, cumulative disease activity, and disease duration in increasing malignancy risk are difficult to separate from the effects of treatment for the disease. Lymphoma (excluding HSTCL) is considered an important identified risk because of consistency of evidence across multiple sources, including data from products in the same class.
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 more likely to have been treated with one or more immunosuppressive medications. There are a number of conflicting studies related to the risk of lymphoma with the use of methotrexate, which is often used in the treatment of RA. Rare spontaneous remissions of lymphoma in RA patients after methotrexate withdrawal suggest a relationship between the drug and lymphoma development. Research has also shown that Epstein Barr virus (EBV) is involved with the development of lymphoma and it has been suggested that

	methotrexate may have a role in the development of EBV-associated lymphomas in RA patients.
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* • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Hepatitis B virus reactivation	
Evidence for linking the risk to the medicine	Drugs that inhibit TNFα have been associated with reactivation of Hepatitis B virus (HBV) in patients who are chronic carriers of the virus. Reactivation of HBV is considered a class effect for these agents. SIMPONI has been investigated in multiple settings. In the postmarketing setting, HBV reactivation has been reported in patients treated with SIMPONI. This is consistent with nonclinical data and published medical literature. Hepatitis B virus reactivation 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	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 IV 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, methotrexate, azathioprine, TNFα inhibitors). Other risk factors/conditions that may predispose a patient for contribute to HBV reactivation include AIDS HIV infection, transplantation (especially bone marrow), and withdrawal from immunosuppressive

	therapies.
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: • *Patient Reminder Card*
Additional PV activities	Additional PV activities: • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Congestive heart failure	
Evidence for linking the risk to the medicine	Congestive heart failure (CHF) has been associated with the use of drugs that inhibit TNFα and is considered a class effect of these agents. SIMPONI has been investigated in multiple settings. In clinical trials, CHF has been reported in patients treated with SIMPONI. Congestive heart failure has also been reported in the postmarketing setting. Congestive heart failure 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	Risk factors for CHF include coronary artery disease, infiltrative cardiac disease, hypertension, valvular disease, arrhythmia, diabetes, infection, use of certain drugs, alcohol use, and increasing age.
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.3 (Contraindications)* • *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimization measures: • *Patient Reminder Card*

Additional PV activities	Additional PV activities: • *P04480* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Autoimmune Processes	
Evidence for linking the risk to the medicine	The development of lupus and lupus-like syndrome is considered a class effect of TNFα inhibitors. SIMPONI has been investigated in multiple settings. In clinical trials, systemic lupus erythematosus (SLE) and lupus-like syndrome have been reported have been reported in patients treated with SIMPONI. Reports of SLE and lupus-like syndrome have also been received in the postmarketing setting and data are consistent with published medical literature. Autoimmune processes 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 factors including genetic, racial, gender, hormonal, and environmental factors have been associated with an increased risk of developing SLE. Specifically, SLE is more common in non-whites, and there is a higher prevalence of the disease in women compared to men, with women of childbearing potential at the greatest risk for developing SLE. Environmental factors such as viruses (eg, Epstein-Barr virus), smoking, ultraviolet light, and silica dust might have a role in the development of SLE.
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: • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Hematologic reactions	
Evidence for linking the risk to the medicine	Drugs that inhibit TNFα have been associated with hematologic reactions, including aplastic anemia, neutropenia, leucopenia, thrombocytopenia, and pancytopenia. SIMPONI has been investigated in multiple settings. In clinical trials, hematologic reactions have been reported in patients treated with SIMPONI. This is consistent with postmarketing reports, published medical literature, and experience with other medicines that also act by inhibiting TNF. Hematologic reactions 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	Hematologic reactions have been associated with various treatment regimens for inflammatory diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-Axial SpA), ulcerative colitis (UC), and polyarticular juvenile idiopathic arthritis (pJIA). Additionally, hematologic reactions may be associated with inflammatory diseases themselves.
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 pharmacovigilance activities	Additional pharmacovigilance activities: • *P04480* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Serious systemic hypersensitivity (including anaphylactic reaction)	
Evidence for linking the risk to the medicine	Hypersensitivity reactions, including serious systemic hypersensitivity reactions, are infrequent events that have been reported with most approved human therapeutic antibodies, including those that act by inhibiting TNFα. SIMPONI has been investigated in multiple settings. Serious systemic hypersensitivity reactions have been reported in the post-marketing setting, including reactions that occurred after the first

	administration of SIMPONI. Serious systemic hypersensitivity (including anaphylactic reaction) is 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	Not known.
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: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *P04480* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Skin cancer	
Evidence for linking the risk to the medicine	Drugs that inhibit TNFα have been associated with an increased risk of skin cancer. Skin cancer is considered a class effect of these agents. SIMPONI has been investigated in multiple settings. In clinical trials, skin cancer (including melanoma) has been reported in patients treated with SIMPONI. Reports of skin cancer (including melanoma and Merkel cell carcinoma) have been received in the postmarketing setting and data are consistent with published medical literature. Skin cancer 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>Melanoma</u> 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 DNA 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 suppression (ie, HIV, organ transplantation) are at higher risk of developing melanomas. <u>Nonmelanoma skin cancer</u> 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, ultraviolet B therapy, psoralen plus ultraviolet A light (PUVA), retinoids, and cyclosporine therapy. <u>Merkel cell carcinoma</u> Although the cause of Merkel cell carcinoma (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.
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: • *P04480* See section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Leukemia	
Evidence for linking the risk to the medicine	Leukemia has been reported in patients with RA who use TNFα inhibitors. However, risk estimation is complicated by the increased background risk for leukemia in RA patients with long-standing, highly active, inflammatory disease. SIMPONI has been investigated in multiple settings. In clinical trials, leukemia has been reported in patients treated with SIMPONI. Reports of leukemia have also been received in the postmarketing setting. Leukemia is considered an important identified risk because of the consistency of evidence across multiple sources.
Risk factors and risk groups	Patients with a history of cancer may have a higher risk of developing leukemia with SIMPONI treatment. 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 more likely to have been treated with one or more immunosuppressive medications. Radiation therapy of the spine in patients with AS has been associated with an increased incidence of leukemia.
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 pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Malignancy	
Evidence for linking the risk to	For some TNFα inhibitors, more cases of malignancies have been

the medicine	observed among subjects receiving those particular TNFα inhibitors compared with control subjects. Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults (up to 22 years of age) who received TNF-blockers (initiation of therapy ≤18 years of age) to treat juvenile idiopathic arthritis, 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 methotrexate, azathioprine, or 6-mercaptopurine. It is not clear whether children with certain autoimmune conditions have an increased risk for malignancy given limited data. SIMPONI has been investigated in multiple settings. In clinical trials, the overall incidence rate of malignancies was similar for SIMPONI-treated subjects and placebo-treated subjects, and was also similar for SIMPONI-treated subjects and the general US population. The only exceptions were the incidence of lymphoma and melanoma. The development of malignancy is considered an important potential risk because the effects attributed to TNFα in published literature, suggesting that certain types of malignancies may be adversely affected by TNFα blockade, may apply to SIMPONI. Of note, lymphoma (excluding HSTCL), skin cancer, and leukemia are considered important identified risks and therefore are not included under this risk of malignancy.

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 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 methotrexate. 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 methotrexate compared with any other DMARD. Smoking is a well-known risk factor in the development of several malignancies and a number of reports link smoking with an increased incidence of lung cancer in patients with RA.
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* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Serious hepatotoxicity	
Evidence for linking the risk to the medicine	There are reports in the published literature of drug-induced liver injury associated with anti-TNFα agents. However, the relationship between SIMPONI and serious hepatotoxicity is not known. SIMPONI has been investigated in multiple settings. As observed with other anti TNFα agents, there have been case reports in the postmarketing setting of serious hepatotoxicity during treatment with SIMPONI. Upon comprehensive review of the clinical data for SIMPONI, there is no obvious increased risk identified for the

	development of serious hepatotoxicity. The observed events of hepatotoxicity in clinical trials were infrequent and often confounded by concomitant medications known to be associated with hepatic adverse reactions. Given the evidence described above, serious hepatotoxicity is considered an important potential risk.
Risk factors and risk groups	Patients with pre-existing liver disease (ie, fibrosis and cirrhosis) would presumably be at increased risk of drug-induced hepatotoxicity, as would patients who are being treated with other hepatotoxic drugs (eg, methotrexate); however, during the clinical trials with SIMPONI, no particular group of patients at risk or risk factors have been identified. Methotrexate has been shown to cause elevations of liver enzymes, but in general these are mild and transient. Additionally, methotrexate has been associated with changes in liver histology including progressive fibrosis that can evolve into cirrhosis. Studies comparing pre- and post-treatment liver biopsies in RA patients treated with methotrexate have shown that while up to 52% of RA patients may develop some hepatic fibrosis during methotrexate therapy, the incidence of cirrhosis has been close to 0. Studies have demonstrated that the risk of chronic liver disease associated with methotrexate increases with larger cumulative doses.
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.8 (Undesirable Effects) and PL section 4* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Exposure during pregnancy	
Evidence for linking the risk to the medicine	Although pregnant women were excluded from SIMPONI clinical trials, some female subjects and female partners of male subjects treated with SIMPONI became pregnant. Exposure to SIMPONI during pregnancy has also been reported in the postmarketing setting, including the published literature. The effects of SIMPONI on the developing human foetus are unknown. SIMPONI has been detected in the serum of infants exposed in utero for up to 6 months following birth. Due to its inhibition of TNF, SIMPONI could affect normal immune responses in the newborn. Consequently, these infants may be at increased risk of infection. Although studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development, given the unknown effects of SIMPONI on the developing human foetus, exposure during pregnancy is considered an important potential risk.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.6 (Fertility, Pregnancy, and Lactation)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* • *CNTO148ART4001* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Serum sickness	
Evidence for linking the risk to the medicine	Administration of monoclonal antibodies (mAbs) has been associated with the development of immune reactions, including serum sickness. SIMPONI has been investigated in multiple settings. Serum sickness been reported in patients treated with SIMPONI in clinical trials and in the postmarketing setting.

	Although serum sickness is usually not life threatening and is an infrequent occurrence, as with most approved human therapeutic antibodies, it is considered as an important potential risk with SIMPONI.
Risk factors and risk groups	Not known.
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: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *P04480* • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Maladministration/administration error	
Evidence for linking the risk to the medicine	Maladministration/administration errors were reported infrequently in the SIMPONI clinical trial program. Reports have also been received in the postmarketing setting. The potential for user error and the possibility of malfunctioning of the product led to the identification of maladministration/ administration errors as an important potential risk with SIMPONI.
Risk factors and risk groups	All individuals who administer SIMPONI (patients, caregivers, and health care providers) are at risk of product failure and other maladministration/administration errors. Patients or caregivers who are not properly selected or trained on how to administer the product, or whose physical limitations impact their ability to administer the product may be at particular risk of maladministration/administration errors.

Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.2 (Posology and Method of Administration)* • *SmPC section 4.4 (Special Warnings and Precautions for Use)* • *SmPC section 6.6 (Special Precautions for Disposal and Other Handling)* 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 post-authorization 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 rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis 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 pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* • *MK-8259-050* See section II.C of this summary for an overview of the post-authorization development plan.

Important Potential Risk: Colon cancer/dysplasia (in ulcerative colitis [UC])	
Evidence for linking the risk to the medicine	Colorectal cancer 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 colorectal cancer. Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF inhibitors, including SIMPONI, to cause immunosuppression affecting host defences 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 patients treated with SIMPONI. Of note, all the cases of colon polyps reported in the UC trials were confirmed to be inflammatory and with no dysplasia. Colon cancer/dysplasia (in UC) 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 colorectal cancer, 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 post-authorization development plan.

Important Potential Risk: Hepatosplenic T-cell lymphoma (HSTCL)	
Evidence for linking the risk to the medicine	Rare post-marketing cases of HSTCL have been reported in patients treated with other TNF inhibitors. Since there is a theoretical risk that HSTCL may also occur with the use of SIMPONI, it is considered an important potential risk.
Risk factors and risk groups	Based on a published series of cases, young men appear to be at a higher risk for HSTCL. Patients who are immunocompromised or undergoing solid organ transplantation appear to be at risk of HSTCL.
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 post-authorization development plan.

Important Potential Risk: Medication error (wrong dose related to different strengths)	
Evidence for linking the risk to the medicine	Medication error (wrong dose related to different strengths) has been reported in the postmarketing setting and is considered an important potential risk for SIMPONI.
Risk factors and risk groups	Factors that contribute to this risk include: • A dose other than that intended is prescribed, dispensed, or administered to or by the patient • Patients whose dose changes • Patients with physical and/or mental challenges (eg, decreased visual acuity).
Risk minimization measures	Routine risk minimization measures:

	• *SmPC section 4.2 (Posology and Method of Administration)* • *SmPC section 4.4 (Special Warnings and Precautions for Use)* • *Packaging design* 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 post-authorization development plan.

Missing information: Use in pediatric patients with ulcerative colitis	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.2 (Posology and Method of Administration)* • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148UCO1001* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with hepatic impairment	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with renal impairment

Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with a past history of latent or active tuberculosis (TB)	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.3 (Contraindications)* • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with concurrent malignancy or a history of malignancy	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with active infections including HIV, hepatitis B, hepatitis C	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with recent prior use of other biologics excluding anti-TNFα agents	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* • *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with concomitant diagnosis of congestive heart failure (CHF) including medically controlled asymptomatic CHF	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.3 (Contraindications)* • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with history of demyelinating disease	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients with a history of lupus or lupus-like syndrome	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *CNTO148ART4002* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Use in patients after recent vaccination with live bacterial or viral vaccine	
Risk minimization measures	Routine risk minimization measures: • *SmPC section 4.4 (Special Warnings and Precautions for Use)* • *SmPC section 4.5 (Interaction with Other Medicinal Products and Other Forms of Interaction)* • *SmPC section 4.6 (Fertility, Pregnancy, and Lactation)* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *None*

Missing information: Long-term safety in adult patients	
Risk minimization measures	Routine risk minimization measures: • *None* Additional risk minimization measures: • *None*
Additional PV activities	Additional PV activities: • *P04480* • *CNTO148ART4002* • *MK-8259-013 (in UC)* • *MK-8259-042 (in UC)* See section II.C of this summary for an overview of the post-authorization 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 post-authorization development plan.

II.C. Post-authorization 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 Post-authorization 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 including opportunistic infections and TB Demyelinating disorders Lymphoma (excluding HSTCL) Congestive heart failure

Study	Purpose of the Study
	Hematologic reactions Serious systemic hypersensitivity (including anaphylactic reaction) Skin cancer Malignancy Serum sickness Long-term safety in adult patients
CNTO148ART4002: Golimumab safety and surveillance program using Optum Research Database	To use a large US health insurance claims database to evaluate the incidence rate of selected outcomes of interest in a cohort of patients with RA, PsA, or AS initiating golimumab, other biologics, or non-biologics; the risks in the golimumab cohort will be compared to those in similar patients in the control cohorts. To address the safety concerns of: Serious infections including opportunistic infections and TB Demyelinating disorders Hypertension (new onset hypertension only) Lymphoma (excluding HSTCL) Hepatitis B virus reactivation Congestive heart failure Autoimmune processes Hematologic reactions Serious systemic hypersensitivity (including anaphylactic reaction) Leukemia Malignancy Serious hepatotoxicity Exposure during pregnancy Serum sickness Serious depression including suicidality Use in patients with hepatic impairment Use in patients with renal impairment Use in patients with a past history of latent or active TB Use in patients with concurrent malignancy or a history of malignancy Use in patients with active infections including HIV, hepatitis B, hepatitis C Use in patients with recent prior use of other biologics excluding anti-TNFα agents Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF Use in patients with a history of demyelinating disease Use in patients with a history of lupus or lupus like syndrome Long-term safety in adult patients

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 analyse 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 analyse 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: An Observational Longitudinal Post Authorization 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 and incident HGD as a composite endpoint • Colectomy for intractable disease • Incident CRC • Incident HSTCL Among patients with UC who discontinue golimumab after achieving remission, describe the duration of remission and potential determinants To address the safety concerns of: Colon cancer/dysplasia (in UC) HSTCL Long-term safety in adult patients (in UC)
CNTO148UCO1001: A Phase 1b open label study to assess the safety and pharmacokinetics of subcutaneously administered golimumab, a human anti-TNFαantibody, in pediatric subjects with moderately to severely active ulcerative colitis	To evaluate the PK 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 concerns of: Use in pediatric patients with UC 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 post-authorization safety study to investigate long-term safety of golimumab in pJIA. To address the safety concerns of: • Serious infections including opportunistic infections and TB • Malignancies • Autoimmune processes • Exposure during pregnancy Secondary objectives will include crude incidence rates of • Demyelinating disorders • Congestive heart failure • Hypertension • Serious hepatotoxicity • Hematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Serum sickness • Hepatitis B virus reactivation • Serious depression including suicidality • Maladministration/administration error • Medication error (wrong dose related to different strengths)
MK-8259-042: A Post-Authorization 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 HGD (hereafter 'advanced colonic neoplasia' [ACN]). To address the safety concerns of: Colon cancer/dysplasia (in UC) HSTCL Long-term safety in adult patients (in UC)
MK-8259-038 (Phase IV, Efficacy)	To evaluate the efficacy of golimumab (full or reduced treatment regimen) versus treatment withdrawal in subjects with nr-Axial SpA who have attained inactive disease while receiving open label golimumab and to characterize the efficacy of golimumab as retreatment upon flare in subjects with nr-Axial SpA.