Data lock point for current RMP	06 April 2023	Version number	27.1

CHMP Opinion Date: 30 November 2023

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RMP Version Number: 27.1
Supersedes Version: 26.1
EDMS Number: EDMS-RIM-1196318

QPPV Name:	Dr. Laurence Oster-Gozet, PharmD, Ph.D.
QPPV Signature:	The Marketing Authorization Holder (MAH) QPPV has either reviewed and approved this RMP or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	27.1
Rationale for submitting an updated RMP	Completion of the following category 3 additional pharmacovigilance activities: - MK-8259-013: A non-interventional observational longitudinal postauthorization safety study of SIMPONI in treatment of ulcerative colitis using Nordic National Health Registries - MK-8259-042: A postauthorization safety study of golimumab in UC using the Spanish ENEIDA Registry
Summary of significant changes in this RMP	<u>Safety specification:</u> Removed the following safety concerns: - Important potential risk "Colon cancer/dysplasia (in ulcerative colitis)" - Missing information "Long-term safety in adult patients with UC" <u>Pharmacovigilance Plan:</u> Removed the following category 3 additional pharmacovigilance activities: - MK-8259-013 - MK-8259-042

Other RMP Versions Under Evaluation:

Not applicable.

Details of the Currently Approved RMP:

Version number of last agreed RMP:	26.1
Approved within procedure	EMEA/H/C/000992/II/0113
Date of approval (Competent authority opinion date)	06 July 2023

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Golimumab
Pharmacotherapeutic group(s) (ATC Code)	L04AB06
Marketing Authorization Holder	Janssen Biologics BV
Medicinal products to which the RMP refers	Golimumab (SIMPONI®)
Invented name(s) in the European Economic Area (EEA)	SIMPONI®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Golimumab is a human monoclonal antibody (mAb) that binds to human tumor necrosis factor alpha (TNFα). Golimumab is an immunoglobulin (Ig) G1κ (G1m[z] allotype) mAb with a molecular weight of approximately 150,000 Daltons. Summary of mode of action Golimumab forms high affinity, stable complexes with both the soluble and transmembrane forms of human TNFα and consequently prevents the binding of TNFα to its receptors. Golimumab neutralizes TNF-induced expression of cell-surface adhesion proteins and secretion of cytokines and chemokines by human endothelial cells. Important information about its composition Golimumab was derived by immunizing mice that were transgenic for part of the human Ig repertoire with human TNFα and applying conventional cell fusion technology to generate a hybridoma cell line that secreted a human mAb termed TNV148. The complementary deoxyribonucleic acid (DNA) molecules encoding the TNV148 mAb heavy chain and light chain variable regions were cloned from the hybridoma cells and combined with coding sequences for human heavy chain (IgG1 isotype, G1m[z] allotype) and human light chain (kappa isotype) constant regions. Transfected cells secreting large amounts of the recombinant version of the mAb, designated golimumab, were identified by extensive screening of supernatants from cell cultures followed by subcloning to identify stably producing, homogeneous cell lines.
Reference to the Product Information	Mod1.3.1/Summary of Product Characteristics (SmPC), Labelling and Package Leaflet (PL)

Indication(s) in the EEA	Current: Rheumatoid arthritis SIMPONI, in combination with methotrexate (MTX), is indicated for: • The treatment of moderate to severe, active rheumatoid arthritis (RA) in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy, including MTX, has been inadequate. • The treatment of severe, active, and progressive RA in adults not previously treated with MTX. SIMPONI, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function. Psoriatic arthritis SIMPONI, alone or in combination with MTX, is indicated for: • The treatment of active and progressive psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy has been inadequate. SIMPONI has also been shown to reduce the rate of progression of peripheral joint damage as measured by x-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function. Ankylosing spondylitis SIMPONI is indicated for the treatment of severe, active ankylosing spondylitis (AS) in adults who have responded inadequately to conventional therapy. Ulcerative colitis SIMPONI is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine or who are intolerant to or have medical contraindications for such therapies. Nonradiographic axial spondyloarthritis SIMPONI is indicated for the treatment of adults with severe, active nonradiographic axial spondyloarthritis (SpA) (AxSpA) (nr-AxSpA) with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs). Juvenile idiopathic arthritis *Polyarticular juvenile idiopathic arthritis:* SIMPONI, in combination with MTX, is indicated for the treatment of polyarticular juvenile idiopathic arthritis (JIA) (pJIA) in children 2 years of age or older who have responded inadequately to previous therapy with MTX.
	Proposed: Not applicable.

Dosage in the EEA	Current: Rheumatoid arthritis 50 mg of SIMPONI given as a subcutaneous (SC) injection once a month, on the same date each month. SIMPONI should be given concomitantly with MTX. Psoriatic arthritis, AS, and nr-AxSpA 50 mg of SIMPONI given as a SC injection once a month, on the same date each month. *Patients with body weight greater than 100 kg* In patients with RA, PsA, AS, or nr-AxSpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse drug reactions (ADRs) with the 100 mg dose compared with the 50 mg dose. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg. Ulcerative colitis *Patients with body weight less than 80 kg* SIMPONI given as an initial dose of 200 mg, followed by 100 mg at Week 2. Patients who have an adequate response should receive 50 mg at Week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at Week 6 and every 4 weeks thereafter. *Patients with body weight greater than or equal to 80 kg* SIMPONI given as an initial dose of 200 mg, followed by 100 mg at Week 2, then 100 mg every 4 weeks, thereafter. Polyarticular JIA *Children with body weight of at least 40 kg* SIMPONI 50 mg administered once a month, on the same date each month, for children with a body weight of at least 40 kg. For children with body weight of at least 40 kg, a 50 mg pre-filled pen or pre-filled syringe is available. *Children with body weight less than 40 kg* The recommended dose of SIMPONI for children with a body weight less than 40 kg with pJIA is 30 mg/m^2 body surface area up to maximum single dose of 40 mg administered once a month, on the same date each month. A dosing table (based upon height and weight) for use with the 45 mg/0.45 mL pre-filled pen for pediatric use is provided in Section 4.2 of the SmPC.
	Proposed: Not applicable.

Pharmaceutical form(s) and strength(s)	Current: SIMPONI is supplied as solution for injection in the following presentations: A single-use prefilled syringe (PFS) containing: • 50 mg golimumab per 0.5-mL syringe • 100 mg of golimumab per 1-mL syringe A single-use prefilled pen containing: • 50 mg golimumab per 0.5-mL pen • 100 mg of golimumab per 1-mL pen A single-use prefilled pen for pediatric use containing: • 45 mg golimumab per 0.45 mL	
	Proposed: Not applicable.	
Is/will the product subject of additional monitoring in the European Union (EU)?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Rheumatoid Arthritis

Incidence:

The incidence of RA varies by country. The median annual incidence observed in south European countries was 16.5 cases per 100,000 persons (Alamanos 2006). For north European countries the median annual incidence observed was 29, and for North American countries, 38 (Alamanos 2006). In Sweden, Eriksson et al studied the Swedish National Patient Register for patients diagnosed with RA between 2006 and 2008; the overall incidence of RA was 41 per 100,000 persons (56 for women and 25 for men) (Eriksson 2013). An Italian study estimated the annual incidence of RA for that country to be 35 per 100,000 persons (95% confidence interval [CI]: 29-42) (Rossini 2014). A study in the United Kingdom (UK) using the Clinical Practice Research Datalink, a database of longitudinal medical records from primary care, reported an incidence of 3.81 (95% CI: 3.61-4.02) per 10,000 person-years in 2014 (Abhishek 2017).

In the United States (US), a study in Olmsted County, Minnesota, included RA data from 1995 to 2007 for residents 18 or older. Similar to the Swedish study, the overall age- and sex-adjusted annual incidence among residents was 40.9 per 100,000 population (Myasoedova 2010).

Prevalence:

The overall world prevalence of RA is approximately 0.5% to 1% (Gibofsky 2012). A population survey for the prevalence of rheumatic diseases in adults was conducted in central Greece. Of 1,705 individuals that responded to the questionnaire, 420 (24.6%) reported rheumatic disease and diagnoses were confirmed by a rheumatologist. In this population, the prevalence of RA was 0.58% (95% CI: 0.32%-0.87%) (Anagnostopoulos 2010).

In the UK, RA is the second most common form of arthritis and the most common inflammatory joint disorder. Estimated number of cases of RA in the UK are listed below (Arthritis Research UK. Rheumatoid Arthritis 2013).

Prevalence of RA in the UK, 2013

Age (Years)	Males (%)	UK Estimate	Females (%)	UK Estimate
16-44	0.02	2,500	0.12	15,100
45-64	0.58	42,900	1.67	126,900
64-74	1.14	27,100	2.56	67,800
75+	2.18	39,100	2.99	85,700
Total Adult Population	**0.44**	**106,500**	**1.16**	**297,600**

Source: Arthritis Research UK. Rheumatoid Arthritis 2013

In the aforementioned study by Myasoedova et al in Olmsted County, Minnesota, the overall age- and sex- adjusted prevalence of RA among individuals who were 18 years of age or older on 01 January 2005 was 0.72%, which represents an increase from the estimates of 0.62% on 01 January 1995 (Myasoedova 2010). When the prevalence of RA on 01 January 2005 was applied to the US population in 2005, it showed that an estimated 1.5 million US adults were affected by RA.

Demographics of the Population in the RA Indication (Age and Sex) and Risk Factors for the Disease:

Globally, the age-standardized prevalence rate of RA was higher in women and increased with age, peaking at 70 to 74 years among women and 75 to 79 years among men in 2017. Although the onset of RA may occur at any time from early adulthood to advanced old age, the number of incident cases reaches its highest level at 50 to 54 years, followed by a declining trend from 55 years onwards (Safiri 2019).

Women are approximately 3 times more likely to develop RA than men (Lipsky 2008). In the Swedish study by Eriksson et al, women had a higher incidence rate in all age categories compared with men, though the difference decreased with age (Eriksson 2013). In the previously described prevalence study in Greece, female to male ratio with RA was defined as 2.3:1 (Anagnostopoulos 2010). In the UK, incidence and prevalence rates appear to be higher for females in all age groups with the exception of the incidence rate in 75-and-over age group (Arthritis Research UK. Rheumatoid Arthritis 2013). A US study reported that the age adjusted prevalence of RA in adults ranged from 0.29% to 0.31% for men and 0.73% to 0.78% for women (Hunter 2017).

Risk Factors

Genetics

Twin and family studies suggest that the risk of disease among relatives of individuals is influenced by shared genetic factors. Studies carried out in Caucasian patients with established and advanced disease indicated an association of RA with alleles encoding a "shared epitope" (called "rheumatoid epitope"). These studies also suggested a significant association of "rheumatoid epitope" with disease severity and outcome (Alamanos 2006).

There is long-standing evidence that specific human leucocyte antigen (HLA) class II genotypes are associated with an increased risk of RA. Most attention has been given to the DR4 and DRB1 molecules of the major histocompatibility complex HLA class II genes. The strongest associations have been found between RA and the DRB1*0401 and DRB1*0404 alleles. Investigations indicate that of the more than 30 genes studied, the strongest candidate gene is PTPN22, a gene that has been linked to several autoimmune conditions (Hinks 2005).

Smoking

A history of smoking is associated with a modest to moderate (1.2 to 2.4 times) increased risk of RA onset (Silman 2001). This relationship between smoking and RA is strongest among people who are anti-citrullinated protein/peptide antibodies-positive, which is a marker of autoimmune activity (Scott 2010). The association also appears to be dose-dependent and is most clear for heavy smokers. The severity and outcome of RA appears also to be influenced by smoking, although it is not clear which clinical characteristics of the disease are related to smoking (Alamanos 2005). There is a prolonged increased risk even after cessation (Carmona 2010).

Reproductive and Breastfeeding History

Most studies have found that women who have never had a live birth have a slight to moderately increased risk of RA. Recent population-based studies have also found that RA is

less common among women who breastfeed. At least 2 studies have observed that women with irregular menses or a truncated menstrual history (eg, early menopause) have an increased risk of RA (Centers for Disease Control and Prevention. CDC: Arthritis). A significantly increased risk of RA has been demonstrated in women whose pregnancies were complicated by hyperemesis, gestational hypertension, or pre-eclampsia (Carmona 2010).

Infectious Agents

It is possible that infectious agents could trigger the development of RA in a genetically susceptible host. Several potential associations of RA with infectious agents have been suggested. They include parvovirus, rubella virus, Epstein-Barr virus, *Borrelia burgdorferi*, and others. The role of infectious agents in the occurrence of the disease remains unclear (Alamanos 2005). Some bacteria such as Proteus and Mycoplasma also show an increased risk of RA (Carmona 2010).

Age

People aged between 40 and 60 years are at higher risk of developing RA (Mayo Clinic. Rheumatoid arthritis: symptoms & causes).

Main Existing Treatment Options:

Rheumatoid arthritis usually requires lifelong treatment, including pharmacologic intervention, physical therapy, exercise, education, and possible surgery. Early aggressive treatment of RA can delay joint destruction. Nonsteroidal anti-inflammatory drugs, corticosteroids, DMARDs, antimalarial medications, several anti-TNFα agents, and other biologics (including white blood cell modulators and interleukin [IL]-6 inhibitors) are used in the pharmacologic management of RA. Other approaches used for the treatment of RA include inhibition of Janus kinases (Mayo Clinic. Rheumatoid arthritis: diagnosis & treatment).

Natural History of RA in the Untreated Population, Including Mortality and Morbidity:

As patients with RA are invariably treated, it is no longer possible to differentiate the effects of treatment from the natural history of the disease (Scott 2007). The natural disease progression of RA results in persistent joint inflammation, progressive joint damage, and continuing functional decline (Scott 2010). As the disease progresses, cartilage and bone within the joint become damaged and surrounding muscles, ligaments and tendons become weak (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2017). Some patients with RA experience periods of disease flare and periods of remission (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2017). A study conducted in Sweden reported that, at baseline, about 95% of RA patients fell into the moderate or severe category and over a period of 3 years of receiving appropriate physician directed care, these proportions changed such that about 25% met the criteria for remission, 10% had low activity, 50% had moderate activity, and about 15% had high activity (Hallert 2006).

Patients with RA have about a 50% increased risk of premature mortality, and their life expectancy is decreased by 3 to 10 years compared with the general population (Myasoedova 2010).

In 2019, the global mortality rate for RA was estimated to be 0.57 deaths per 100,000 population (0.44 to 0.67) (Institute for Health Metrics Evaluation 2020). A meta-

analysis by Dadoun et al found a pooled incident mortality rate (IMR) in RA of 2.7 per 100 person-years (95% CI: 2.2-3.3) (Dadoun 2013). The rates ranged from 1.0 per 100 person-years to 5.2 per 100 person-years. The analysis revealed a significant decrease in IMR over 3 periods. The estimated pooled IMR was 4.7 per 100 person-years (95% CI: 4.0-5.4) for studies starting before 1970, 3.0 per 100 person-years (95% CI: 2.3-4.0) for those starting between 1970 and 1985; and 2.0 per 100 person-years (95% CI: 1.3-2.8) for those starting after 1985. Older age at diagnosis and longer length of follow-up were found to be significant factors for higher IMR. The mean standardized mortality ratio (SMR) for 8 studies was 2.01 (95% CI: 1.99-2.03). The Norfolk Arthritis Register in the UK reported that for patients who had been followed for 20 years, the age and sex SMR was 1.25 (95% CI: 1.11-1.42) and that older age at onset and male gender were associated with increased risk of death during that time period (Gwinnutt 2017).

Important Comorbidities:

Comorbidities that occur frequently in patients with RA include depression, asthma, cardiovascular events (myocardial infarction, stroke), solid malignancies, and chronic obstructive pulmonary disease (Dougados 2014).

Indication: Psoriatic Arthritis

Incidence:

A meta-analysis of 28 studies reported a pooled incidence of 8.3 per 100,000 person-years (95% CI: 4.1-16.7) (Scotti 2018). A meta-analysis of 10 studies reported incidence rates ranging from 0.27 per 100 person-years to 2.7 per 100 person-years among patients with psoriasis (Alinaghi 2019).

Prevalence:

A meta-analysis of 28 studies reported a pooled prevalence of 0.13% (95% CI: 0.11%-0.16%) (Scotti 2018). Globally, the prevalence of PsA ranges from 0.04% to 1.2%, depending on the population studied (Gladman 2005a). A systematic review of 10 studies estimated the prevalence of PsA in Europe to be 0.19% (95% CI: 0.16%-0.32%) (Stolwijk 2016). In a study conducted using Kaiser Permanente Northern California Data, the number of persons with one or more International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes for PsA between 1996 and 2009 was 5,187, corresponding to a point prevalence of 12.6 (95% CI: 11.6-13.7) per 100,000 persons, standardized to the age and sex distribution of the 2000 census on 31 December 2009 (Asagari 2013). A meta-analysis of 266 studies reported a pooled proportion of PsA among patients with psoriasis of 19.7% (95% CI: 18.5%-20.9%) with some estimates as high as 30% (Alinaghi 2019; Mease 2013).

A cross-sectional study using The Health Information Network (THIN) database from the UK found that among 4.8 million patients aged 18 to 90 years, between 1994 and 2010, a total of 9,045 patients had at least 1 medical code for PsA, giving an overall prevalence of 0.19% (95% CI: 0.185-0.193). The prevalence by age and sex are reported in the table below (Ogdie 2013).

Prevalence by Age and Sex of PsA in the THIN Database (1994-2010)

Age	Men		Women		All	
(years)	PsA (n)	Prevalence (%)	PsA (n)	Prevalence (%)	PsA (n)	Prevalence (%)
18-29	316	0.05	353	0.05	669	0.05
30-39	916	0.17	819	0.16	1,735	0.16
40-49	1,157	0.29	952	0.26	2,109	0.28
50-59	1,115	0.36	1,092	0.36	2,207	0.36
60-69	675	0.31	733	0.32	1,408	0.31
70-80	334	0.23	380	0.20	714	0.21
80-90	75	0.12	128	0.10	203	0.11
All	**4,591**	**0.20**	**4,461**	**0.18**	**9,045**	**0.19**

Demographics of the Population in the PsA Indication (Age and Sex) and Risk Factors for the Disease:

Anyone can develop PsA but it occurs most often in adults between the ages of 30 and 50 years (Mayo Clinic. Psoriatic arthritis: symptoms & causes).

Overall, men and women are affected by PsA with equal frequency, though the actual male: female ratio may vary depending upon the subset in question. The demographic profile is probably consistent with that of psoriasis.

Risk Factors

Family History

Many people with PsA have a parent or sibling with the disease (Mayo Clinic. Psoriatic arthritis: symptoms & causes). Studies have suggested that there is a high risk for PsA among first-degree relatives. Associations of HLA with PsA have been demonstrated particularly for class 1 alleles at the B and C loci. In addition to being associated with the disease, HLA antigens have been identified as prognostic markers for the progression of clinical damage in PsA (Gladman 2009).

Psoriasis

Approximately 20% to 30% of patients with psoriasis eventually develop PsA (Ocampo 2019). The single greatest risk factor is psoriasis lesions on nails. It has been suggested that an infectious agent may trigger the psoriatic process, and the immunological response seen in patients with both psoriasis and PsA may be the result of mimicry between streptococcal antigens and epidermal autoantigens. The exacerbation of psoriasis and PsA seen in the context of acquired immunodeficiency virus infections suggests that human immunodeficiency virus (HIV) may play a role (Gladman 2009).

Main Existing Treatment Options:

The treatment of PsA is similar to the treatment of RA and focuses on controlling inflammation in the affected joints to prevent joint pain and disabilities. Nonsteroidal anti-inflammatory drugs, intra-articular steroid injections, DMARDs, immunosuppressants, several anti-TNFα agents, and other biologics (including IL-12/23 inhibitors and IL-17 inhibitors) are used in the pharmacologic management of PsA (Mayo Clinic. Psoriatic arthritis: diagnosis & treatment).

Natural History of PsA in the Untreated Population, Including Mortality and Morbidity:

Because observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population and to differentiate the effects of treatment from the natural history of the disease. Spondylitis (inflammation of the vertebra) has been reported to be present in 40% of PsA patients, and 87% have psoriatic lesions of the nails (Gladman 2005b). As the disease progresses, 20% of patients develop a very destructive disabling form of arthritis and 47% sustain erosive changes after 2 years of disease (Gladman 2009). It has been reported that for patients who have been followed for more than 10 years, 55% had 5 or more deformed joints (Gladman 2005b).

Patients who were entered into the PsA database at the Royal National Hospital for Rheumatic Diseases between 1985 and 2007 were included in a study to examine mortality of PsA patients. Of 453 patients with PsA (232 men, 221 women), 37 deaths were reported (16 men and 21 women). The SMR was 67.78% for men (95% CI: 38.79-110.22) and 97.01% for women (95% CI: 60.05-148.92). The overall SMR for the PsA cohort was 81.82% (95% CI: 57.61-112.78). The leading causes of death in this cohort were cardiovascular disease (38%), diseases of the respiratory system (27%), and malignancy (14%) (Buckley 2010).

Mortality results from a literature review by Arumugam and McHugh are illustrated in the table below (Arumugam 2012).

Mortality in PsA

Study and Location	Year Published	No. Patients	Controls	Findings
Coulton, UK	1989	40	n/a	No deaths
Wong, Canada	1997	428	General population	SMR 1.62
Shbeeb, US	2000	66	General population	Similar survival
Alamanos, Greece	2003	221	n/a	4 deaths
Ali, Canada	2007	680	General population	SMR 1.36
Wilson, US	2009	147	General population	SMR 0.91
Buckley, UK	2010	453	General Population	SMR 0.82

Key: n/a=not applicable; No.=number; SMR=standardized mortality ratio; UK=United Kingdom; US=United States.

Important Comorbidities:

Comorbidities that occur frequently in patients with PsA include diabetes mellitus, obesity, metabolic syndrome (or components of it), cardiovascular disease, osteoporosis, inflammatory bowel disease (IBD), autoimmune eye disease, non-alcoholic fatty liver disease, fibromyalgia, and depression (Haddad 2017).

Indication: AxSpA (including AS and nr-AxSpA)

Axial SpA is the term used for a classification of inflammatory rheumatic diseases that includes AS and nr-AxSpA. The Assessment of SpondyloArthritis International Society introduced the classification of nr-AxSpA in 2009. Literature regarding the nr-AxSpA patient population is limited at this time. However, patients with nr-AxSpA are very similar to those with AS with the exception that the sacroiliac joints of the pelvis have little to no changes by x-ray in nr-AxSpA. Many patients initially diagnosed as having nr-AxSpA or undifferentiated SpA may subsequently develop AS. Therefore, given the similar classification and the nature of these diseases, the epidemiology information is presented together for AS and nr-AxSpA in the following sections and where separate information is available, it is provided.

Incidence:

The incidence of AS is reported to be between 0.5 to 14 per 100,000 population per year (Jacobs 2008; Stolwijk 2012). Estimated rates of the incidence for AS vary significantly among populations. A study from Norway reported an annual incidence of AS between 1982 to 1993 of 14.1 per year in the town of Tromsø compared with 5.2 per year in the surrounding rural region (Bakland 2005). A study from Greece reported that incidence rates were higher in the age group 35 to 44 years for men and in the age group 25 to 34 years for women. A US study reported an age- and sex-adjusted incidence of 3.1 per 100,000 population (95% CI: 2.5-3.8) in adults (Wright 2015).

Prevalence:

The prevalence of AS has been estimated to vary between 0.01% and 1.84% depending on the geographical region being studied (Healey 2011; Stolwijk 2012). A review of the prevalence of AS in Europe estimated the mean prevalence to be 23.8 per 10,000 population (Dean 2014). A US study of medical and pharmacy claims data reported a prevalence of 0.09% for adults in 2016 (Walsh 2019). In Germany, the age-specific prevalence of self-reported, doctor-diagnosed AS in the general population was reported as follows: age 18 to 44 years, 0.6%; age 45 to 64 years, 1.6%; age 65 to 74 years, 1.9%; age 75 to 79 years, 1.4%; total 1.1% (Westhoff 2009). In Sweden, the point prevalence of AS in 2009 was estimated at 0.18% for the population aged between 16 and 64 years (Exarchou 2015).

A US study that examined radiographs obtained from the National Health and Nutrition Examination Survey I (NHANES I) provided prevalence estimates for sacroiliitis, an important component of the AS case definition. The prevalence of moderate to severe sacroiliitis was 0.4% among men aged 25 to 34 years; 0.6% among men aged 65 to 74 years; and 0.4% among women aged 65 to 74 years (Dillon 2011).

One epidemiologic study has estimated the prevalence of AS and nr-AxSpA in the US to be 0.35% (95% CI: 0.18%-0.554%) and 0.35% (95% CI: 0.18%-0.554%), respectively (Strand 2013).

Demographics of the Population in the AxSpA Indication (Age and Sex) and Risk Factors for the Disease:

The symptoms of AxSpA are usually first observed in the late adolescence or early adulthood. In a US study, the mean age at diagnosis was reported as 35 years, with a range of 19 to 69 years and a mean (±standard deviation) age of symptom onset of 28.7 (±9.2) years (Wright 2015). In

an international, multicenter, observational study, the median age at onset of axial symptoms in patients with AxSpA was 26 years (IQR 20-34) (Boel 2022). The male: female ratio among patients with AS is approximately 3.8:1 (Dean 2014). The male: female ratio has been estimated to be 2:1 for radiographic AxSpA and 1:1 for nr-AxSpA (Sieper 2017). A multicenter study of men and women in France with nr-AxSpA showed women with early nr-AxSpA had greater disease activity and worse functioning despite fewer radiologic abnormalities than men (Tournadre 2013).

Risk Factors

The risk factors associated with AxSpA, including AS and nr-AxSpA, include being male, age (onset generally occurs in late adolescence or early adulthood), and having the HLA-B27 gene (Mayo Clinic. Ankylosing spondylitis: symptoms & causes). Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking can predict future radiographic damage in patients with early SpA (Slobodin 2015).

Main Existing Treatment Options:

The goal of treatment is to relieve pain and stiffness and prevent or delay complication and spinal deformity. Ankylosing spondylitis treatment is most successful before the disease causes irreversible damage to joints.

Nonsteroidal anti-inflammatory drugs and several anti-TNFα agents are used in the pharmacologic management of AS and nr-AxSpA (Mayo Clinic. Ankylosing spondylitis: diagnosis & treatment; Ward 2016). In addition, inhibition of IL-17 has been shown to be effective for the treatment of AS (Mayo Clinic. Ankylosing spondylitis: diagnosis & treatment).

Most people with AS or nr-AxSpA do not need surgery. However, it may be recommended if the patient has severe pain or joint damage, or if a hip joint is so damaged that is needs to be replaced.

Natural History of AxSpA in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of AxSpA in the untreated population, and to differentiate the effects of treatment from the natural history of the disease. Many people with AS have mild, intermittent episodes of back pain. Symptoms can also be severe with ongoing pain accompanied by loss of flexibility of the spine. In the most severe cases, long-term inflammation leads to calcification that causes 2 or more bones of the spine to fuse (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2016). In the European population, it has been reported that 42% also had peripheral arthritis; enthesitis was present in 38% of AS patients, and uveitis in 24% (Benegas 2012). In patients with severe involvement, which is approximately 33% of the AS population, most loss of function and damage occurs during the first 10 years of disease (Braun 2002).

For nr-AxSpA, many patients will progress to radiographic AxSpA or AS after years of disease. This radiographic progression can be seen in about 10% of patients over 2 years of follow-up on average and in up to 20% over 2 years among those with elevated C-reactive protein or active inflammation on magnetic resonance imaging. Some patients with nr-AxSpA will suffer from the disease for decades, and probably for life, without any evidence of radiographic damage. It is also possible that some patients with nr-AxSpA may experience remission (Slobodin 2015).

A total of 677 patients with AS were followed at a hospital in Norway from 1977 to May 2009. Patients were matched by sex, age, and postal area to 3 controls from the general population. The crude mortality among patients with AS was 14.5% (98 patients); SMR was only significantly increased among male patients compared with female patients (1.63% vs 1.38%, $p<0.001$). Circulatory disease was the most frequent cause of death (40.0%), followed by malignant (26.8%) and infectious (23.3%) diseases (Bakland 2011). Data on mortality associated with nr-AxSpA are not available.

Important Comorbidities:

Comorbidities that occur frequently in patients with AS and nr-AxSpA or with consistently higher prevalence than controls include hypertension, hyperlipidemia, obesity, depression, and heart failure (Zhao 2020).

Indication: Ulcerative Colitis

Incidence:

Ng (2017) conducted a systematic review of studies published between 1990 and 2016 which include worldwide incidence rates of UC. The annual incidence rates varied by geographic region with estimates ranging from 0.97 to 57.9 per 100,000 person-years in Europe and 8.8 to 23.14 per 100,000 person-years in North America. The highest reported incidence rates were in the Faroe Islands (57.9 per 100,000 person-years) and Canada (23.14 per 100,000 person-years). (Ng 2017)

In a study to evaluate the incidence of UC in the Uppsala Region, Sweden, all new UC patients were prospectively registered during 2005 to 2006 and during 2007 to 2009. The mean overall incidence for the time period was 20.0 (95% CI: 16.1-23.9) cases per 100,000 inhabitants (Sjöberg 2013). Another regional Swedish study reported an incidence rate of 18.1 per 100,000 population in 2010 (Eriksson 2017). A national study conducted in Denmark, which included all ages, estimated the incidence rate of UC in 2011 to be 22.4 (95% CI: 20.6-24.2) per 100,000 person-years for women and 23.5 (95% CI: 22.7-25.5) per 100,000 person-years for men. This is an increase from 1995 when the rates were 13.9 (95% CI: 12.1-15.0) per 100,000 person-years for women and 13.6 (95% CI: 11.9-14.8) per 100,000 person-years for men. (Nørgård 2014). In the Netherlands, the incidence rate has been reported at 17.2 per 100,000 person-years (de Groof 2016).

In the US, the incidence of UC per 100,000 person-years was reported in the Nurses' Health Study I and the Nurses' Health study II, which include over 20 years of data, as follows: ages under 30 years, 12.9; ages 30 to 39 years, 9.1; ages 40 to 49 years, 6.9; ages 50 to 59 years, 7.4; ages 60 to 69 years, 9.4; ages 70 years and older, 6.2. The age adjusted incidence of UC per 100,000 person-years ranged from 6.2 to 12.9. (Khalili 2012)

Prevalence:

In Europe, the prevalence of UC ranges from 2.4 to 294 per 100,000 persons (Burisch 2013). One study conducted in Spain reported the prevalence of UC in 2012 as 99.84 per 100,000 population (Lucendo 2014). In the Netherlands, the point prevalence of UC has been reported as 225.6 per 100,000 population for 2004 to 2010 (de Groof 2016). A regional study in Sweden reported the point prevalence for 2010 to be 474 (95% CI: 444-506) per 100,000 inhabitants (Eriksson 2017).

The aforementioned study by Ng et al also analyzed prevalence rates of UC in the literature. The estimates ranged from 0.002% to 0.505% in Europe and 0.14% to 0.29% in North America. Prevalence rates were highest in Norway (0.51%) and the US (0.29%) (Ng 2017).

Kappelman et al (2013) estimated the prevalence of UC in the US to be 0.26% in 2009 based on data from the PharMetrics Choice Patient-Centric Database. After standardizing the data according to 2009 US census data, the authors estimated that approximately 593,000 Americans had UC.

Demographics of the Population in the UC Indication (Age and Sex) and Risk Factors for the Disease:

Ulcerative colitis is most commonly diagnosed in late adolescence and early adulthood, but the diagnosis may occur at any age. One US study using pharmaceutical claims data reported an incidence of 22.9 per 100,000 population for those >60 years and 2.4 per 100,000 population for those <18 years (Keyashian 2019). Some studies of UC have reported sex-related differences in late-onset disease. Men are significantly more likely than women to be diagnosed in the fifth and sixth decades of life. A regional study conducted in Spain reported the incidence rate for UC in women was 2.7 per 100,000 population and 5.1 per 100,000 population in men for 2007 to 2008 (Cueto Torreblanca 2017).

Risk Factors

Risk factors for UC include age (the onset of the disease usually being before the age of 30), being white or of Ashkenazi Jewish descent, having a family history of the disease, and having used isotretinoin (Mayo Clinic. Ulcerative colitis: symptoms & causes). A high-fat diet may also slightly increase the chance of developing UC (National Institute of Diabetes and Digestive and Kidney Disease). There is also evidence that use of NSAIDs, oral contraceptives, and antibiotics may also be associated with an increased risk of UC (Ye 2015).

Main Existing Treatment Options:

The goal of medical treatment is to reduce the inflammation that triggers signs and symptoms of UC. In the best cases, this may lead not only to symptom relief but also to long-term remission. Anti-inflammatory drugs, immunosuppressants, anti-TNFα agents, and other biologics are used in the pharmacologic management of UC. Other approaches used in the treatment of UC include antagonism of integrin receptors. In addition, medications such as antibiotics, anti-diarrheals, pain relievers, and iron supplements may be used in the treatment of UC.

If diet, lifestyle changes, or drug therapy do not relieve signs and symptoms of UC, surgery may be recommended. Surgery can often eliminate UC but usually means removing the entire colon and rectum (Mayo Clinic. Ulcerative colitis: diagnosis & treatment).

Natural History of UC in the Untreated Population, Including Mortality and Morbidity:

Since observational studies generally include a treated population, it is difficult to describe the course of the disease in the untreated population and to differentiate the effects of treatment from the natural history of the disease. The natural course of UC is characterized by periods of flare alternating with periods of remission, and disease activity can decrease over time (Cosnes 2011). A study conducted in Denmark reported that after the first 2 years of follow-up, approximately 50% of patients were in remission, and the proportion of patients with active disease gradually reduced to 30%. There was a cumulative probability of clinical relapse of 81.6% after 5 years. In adults with UC, extension from the initial location was reported to vary from 10% to 19% of patients after 5 years of disease and from 11% to 28% after 10 years (Duricova 2014).

A prospective IBD register in the catchment area of Finland followed UC patients from 1986 to 2007. The authors found an SMR of 0.90 (95% CI: 0.77-1.06). For cause-specific mortality, the risk of death in diseases of the digestive system was increased, although not significantly in UC (SMR: 2.1). Compared with the background population, there were significantly fewer deaths due to mental and behavioral disorders due to use of alcohol (Manninen 2012).

Important Comorbidities:

Comorbidities that occur frequently in patients with UC include uveitis, episcleritis, arthritis, hepatobiliary disorders, infections such as *Helicobacter pylori*, celiac disease, obesity, cardiovascular conditions (including venous thromboembolism and atherosclerosis), and anxiety and mood disorders (Burisch 2013; Román 2011).

Indication: Polyarticular JIA

Incidence:

Juvenile idiopathic arthritis is considered to be the most common rheumatic disease of childhood. JIA includes 6 categories of chronic pediatric arthritis: systemic onset, oligoarticular, polyarticular, enthesis-related, psoriatic arthritis, and undifferentiated arthritis. In Canada, the incidence of JIA was estimated at 8.47 per 100,000 population (95% CI: 7.93-9.05) in 2011/2012 (Shiff 2019). One US study reported an overall age- and sex-adjusted incidence of 10.3 per 100,000 population (95% CI: 7.9-12.7) (Krause 2016). In Sweden, the incidence of JIA has been estimated to be 12.8 per 100,000 children <16 years (Berthold 2019). A systematic review of 29 studies reported pJIA incidence to range from 0 to 8.9 per 100,000 population, with an age and gender standardized pooled incidence of 1.6 per 100,000 population (95% CI: 1.5-1.7) (Thierry 2014). Studies distinguishing rheumatoid factor (RF)+ from RF- pJIA reported pooled incidences of 0.4 per 100,000 children (95% CI: 0.3-0.5) and 1.0 per 100,000 children (95% CI: 0.9-1.2), respectively (Thierry 2014). In a Swedish study, 21% of JIA was estimated to be RF+ or RF-, corresponding to a derived incidence of 2.7 per 100,000 children (Berthold 2019).

Prevalence:

Prevalence of pJIA ranges from 1.6 to 54.2 per 100,000 population with a pooled prevalence of 6.3 per 100,000 population (95% CI: 5.7-6.9). The wide range has been attributed to diagnostic difficulties, new diagnostic criteria and differing definitions developed over time, various means of case ascertainment, health care resources and increasing knowledge, and small studies leading to chance variation in rates (Thierry 2014). The prevalence of rheumatoid factor-positive pJIA in Europe has been estimated at 4.2 per 100,000 population based on data collected from registries and the published medical literature (Orphanet Report Series 2019). Approximately 5% of children with JIA are diagnosed with the psoriatic form of the disease (Stoll 2020).

Demographics of the Population in the pJIA Indication (Age and Sex) and Risk Factors for the Disease:

More females than males are affected by JIA; however, the sex distribution varies by subtype. There is a female predominance in the oligoarticular and polyarticular subtypes, an even distribution of sexes in the systemic subtype, and a male predominance in the enthesitis-related arthritis subtype. A systematic review of the published medical literature reported a pooled incidence rate of 10.0 (95% CI: 9.4-10.7) for girls and 5.7 (95% CI: 5.3-6.2) for boys, and a pooled prevalence rate of 19.4 (95% CI: 18.3-20.6) for girls and 11.0 (95% CI: 10.2-11.9) for boys for JIA (Thierry 2014). The peak age of onset of JIA is 2 to 3 years of age, with a second peak in mid adolescence (Stoll 2020). In North America, the Childhood Arthritis and Rheumatology Research Alliance registry reported a racial distribution for JIA of 93% white, 5% African American, and 3% Asian. African American and Asian patients also tended to have an older mean age of onset, 8.7 and 7.7 years respectively, compared to whites, 6.4 years (Ringold 2013).

<u>Risk Factors</u>

Risk factors for pJIA include genetic susceptibility and environmental triggers; however, the mechanism remains unclear (Huang 2012). It has also been reported that the incidence of JIA

is higher in urban areas and in families with higher incomes than controls. Winter is the peak time of year for the reported onset of symptoms (Oberle 2014). Possible environmental risk factors include infectious agents, antibiotic exposure, and Cesarean-section delivery (Horton 2019). Abnormalities in microbiota have also been implicated as possible risk factors for JIA (Arvonen 2016).

Main Existing Treatment Options:

The management of pJIA is based on a combination of pharmacological management, physical and occupational therapy, and psychosocial support. Nonsteroidal anti-inflammatory drugs, corticosteroids, intra-articular steroid injections, DMARDs, anti-TNFα agents, and other biologics (including T-cell costimulation and IL-6 inhibitors) are used in the treatment of pJIA (Gowdie 2012; Hinze 2015; Onel 2022; Ringold 2019).

Natural History of JIA and pJIA in the Untreated Population, Including Mortality and Morbidity:

The disease course and prognosis of JIA remain variable but have improved with the development of new therapies. In a large single-center study in Spain, 69% of JIA patients attained clinical remission according to the Wallace criteria over a 9-year follow-up period; among pJIA patients, this estimate was 59% (Castillo-Vilella 2021). Compared to children with involvement of fewer joints, children with pJIA (defined as arthritis affecting 5 or more joints during the first 6 months of disease) tend to have a more refractory course of disease. In addition, children with pJIA are at increased risk for joint damage, resulting in poorer functional outcomes and decreased quality of life (Oberle 2014).

The most common feature of all JIA subtypes is arthritis, which is clinically characterized by joint effusion, joint line tenderness and warmth, restricted range of movement, and limitation of movement secondary to pain. Systemic symptoms of pJIA can include fatigue, weight loss, anemia, and anorexia. Growth abnormalities can complicate pJIA and result in bony overgrowth, prematurely fused epiphyzes, and limb length discrepancies (Gowdie 2012). Additionally, patients may experience other physical disabilities, vision loss including blindness, and mental health issues. Uncontrolled arthritis can progress to contractures, limited range of motion, and significant disability (Crayne 2018).

Children with jPsA tend to have more involvement of the wrists and small joints of the hands and feet than patients with oligoarticular JIA. They also have a more complicated course of disease with an increased likelihood of extension into polyarticular disease (Stoll 2020).

A US study of patients classified as having juvenile RA, followed from 1960 to 2013, reported 4 deaths over 2187.7 person-years of follow-up, which was marginally higher than expected (Krause 2016). The British Society for Paediatric and Adolescent Rheumatology (BSPAR) Etanercept Cohort Study and Biologics for Children with Rheumatic Disease study in the UK reported a mortality incidence rate of 1.1 (95% CI: 0.5-2.0) per 1,000 person-years with an SMR of 2.8 (95% CI: 1.4-5.2) for JIA patients (Davies 2017). A population study conducted in Finland that followed all patients with JIA from 2000 to 2015 reported a cumulative mortality rate of 0.6% (95% CI: 0.3-1.2) for JIA patients compared with 0.6% (95% CI: 0.4-1.0) for controls (Kyllönen 2019).

Important Comorbidities:

Comorbidities that occur frequently in patients with pJIA include uveitis, growth abnormalities, and psychosocial factors (Crayne 2018; Gowdie 2012).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
In cynomolgus monkeys, no signs of toxicity considered to be golimumab-related were observed with once-weekly intravenous (IV) doses or twice weekly SC doses up to 50 mg/kg for up to 6 months of treatment (9 months of exposure). In the 6-month IV study, a slight dose-dependent increase in circulating lymphocytes and a slight decrease in the humoral immune response to the T-cell dependent neoantigen keyhole limpet hemocyanin (KLH) was seen. In the 6-month SC toxicology study, a slight increase in circulating lymphocytes similar to that seen in the 6-month IV study was observed. These effects were not considered to be toxicologically significant. In mice, no signs of toxicity considered to be related to the inhibition of TNFα were observed with weekly doses of anti-mouse TNFα mAb (cV1q) up to 40 mg/kg for 6 months.	No toxicities related to the inhibition of TNFα were observed in studies of cynomolgus monkeys and mice. There is a large clinical safety margin relative to the maximum cynomolgus monkey exposure (up to 560 times relative to the human dose and up to 1,000 times the human exposure). The nonclinical data do not indicate a safety concern for humans.
Reproductive toxicity	
Golimumab does not bind to human reproductive tissues in vitro. Young adult cynomolgus monkeys exposed to golimumab at doses up to 50 mg/kg weekly IV or twice weekly SC for up to 6 months showed no toxicity of the reproductive organs (spermatogenesis was not evaluated). Fertility studies have not been conducted with golimumab in cynomolgus monkeys. Fertility studies have been conducted in mice using cV1q. In the mouse fertility study, there was a slight reduction in the number of male mice that mated (91% versus 100% in controls) and a reduction in the number of successful pregnancies (fertility index 76% versus 92% in controls). This reduction is only slightly outside of the test facility historical background ranges; semen parameters (sperm motility, count, and density) were not affected by treatment. Therefore, the apparent reduction in the fertility index was not considered to be due to a reduction in male fertility.	Results of reproductive toxicity studies suggest that inhibition of TNF is unlikely to affect human male or female fertility.

Key Safety Findings	Relevance to Human Usage
Developmental toxicity	
No developmental defects were seen in monkeys from mothers exposed to golimumab during the embryonic period (gestation day [GD] 20 through GD 50) or during the fetal period (GD 50 through birth [approximately GD 165]) and for the first 33 days of lactation at doses up to 50 mg/kg SC twice weekly. Fetuses were exposed to golimumab during gestation and the fetal exposure increased with gestational age during the fetal period. Low levels of golimumab were secreted in breast milk (350-fold lower than in maternal serum). Dosing of pregnant cynomolgus monkeys with golimumab produced no maternal or fetal toxicity. Exposure of developing monkeys to golimumab during gestation and during the postnatal period produced no morphological abnormalities in the fetuses and no structural or functional defects in the neonates. Neonatal immune competence, as determined by the ability to mount a humoral immune response to the T-dependent neoantigen KLH and a delayed-type hypersensitivity skin reaction, were unaffected by exposure to golimumab during pre- and postnatal development. In pregnant mice dosed with cV1q there was no maternal toxicity and no developmental defects in the offspring. A slight reduction in the humoral immune response to sheep red blood cells was observed in the female offspring from mothers exposed to cV1q at 40 mg/kg weekly IV in one study, but this was not repeated in a second study.	The developmental studies conducted in cynomolgus monkeys with golimumab and in mice with cV1q have shown no maternal toxicity and no developmental abnormalities in the offspring. The cynomolgus monkey studies showed that fetuses are exposed to golimumab during the fetal period and that exposure increases with gestational age. This profile is expected to be similar in humans and is similar to that of endogenous IgG antibodies. It is expected that human infants born to golimumab-treated mothers will have golimumab in their serum at birth and that TNF will be inhibited until the serum concentration falls below a pharmacologically relevant level. Golimumab may be secreted in small amounts in breast milk.
Genotoxicity	
No genotoxicity studies were conducted.	
Carcinogenicity	
The risk of reduced tumor immune surveillance resulting in susceptibility to certain tumors (lymphomas and skin cancer) is a safety concern for immune-modulating drugs in general. No tumors were detected in monkeys dosed with golimumab for up to 6 months or in mice dosed with cV1q for 6 months. Rodent 2-year carcinogenicity studies have not been conducted because this bioassay is a poor predictor of malignancy due to immune suppression. Mice that have been genetically modified to lack TNF and wild-type mice dosed with anti-mouse TNF inhibitors have not shown an increased incidence of tumors (Bugelski 2010).	There is a theoretical risk of malignancy associated with administration of golimumab based on the clinical experience with TNF inhibitors and other immune suppressive drugs.

Key Safety Findings	Relevance to Human Usage
Other toxicity-related information or data	
Risk of infection	
The risk of infection is a safety concern for immune-modulating drugs in general. In the 6-month toxicity studies in cynomolgus monkeys, there was a slight decrease in the humoral immune response to KLH. One golimumab-treated animal developed disseminated histoplasmosis. In the mouse developmental study, there was a slight decrease in the humoral immune response to sheep red blood cells. Published rodent studies suggest that inhibition of TNF may lead to a reduction in the host protective immune responses to viral, bacterial, intracellular protozoa, and fungal pathogens (Martin 2012)	Nonclinical studies have shown that inhibition of TNF may be associated with a slight suppression of immune responses to certain antigenic challenges. The single incidence of histoplasmosis in a golimumab-treated monkey cannot be definitively linked to golimumab treatment, although increased susceptibility to infections, including opportunistic infections has been identified clinically.

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1 Brief Overview of Development

The clinical development program for golimumab includes trials in rheumatological indications (RA, PsA, AS, and nr-AxSpA, pJIA) and in subjects with UC.

In an exploratory clinical trial involving subjects with severe persistent asthma (C0524T03), more subjects treated with golimumab developed malignancies compared with control subjects (SmPC, Sections 4.4 [Special warnings and precautions for use] and 4.8 [Undesirable effects]). Therefore, data from trial C0524T03 are included in Module SIII.2 (Clinical Trial Exposure) and Module SVII.3 (Details of Important Identified Risks, Important Potential Risks, and Missing Information).

SIII.2 Clinical Trial Exposure

Exposure to golimumab in the clinical trials population is summarized in Tables SIII.1 through SIII.28 for all subjects by duration, age and sex, dose, and ethnic origin.

Data are presented for (1) the controlled portions of clinical trials and (2) through the end of the reporting period (ie, all portions of clinical trials including open-label extensions).

Trial design (eg, duration of the placebo-controlled portion of the trial, start of the open-label extension, early escape to active treatment), and varying data cut-offs for each trial account for the differences in the numbers of subjects treated with golimumab, as shown in the tables.

Exposure in the Controlled Portions of Clinical Trials

Data from the following trials are included in the tables describing exposure in the controlled portions of clinical trials:

- SC/IV Phase 2 and 3 trials in the rheumatologic indications (RA, PsA, AS, and nr-AxSpA): C0524T02, C0524T05, C0524T06, C0524T11, C0524T12, CNTO148ART3001, C0524T28, C0524T08, C0524T09, P07642, C0524T29, CNTO148PSA3001, and CNTO148AKS3001.
- SC Phase 2b trial in asthma (C0524T03)
- SC/IV Phase 2/3 trials in UC (C0524T16 and C0524T17)

The duration of exposure was calculated as the time from the first dose to the date of the last visit in the controlled period. If a subject discontinued the study agent prior to the last visit date in the controlled period, then exposure for that subject was calculated as the time from the first dose to the last dose during the controlled period.

During the placebo-controlled portions of golimumab clinical trials noted above, a total of 4,560 subjects were exposed to golimumab (Tables SIII.1 through SIII.12).

Exposure to golimumab during the controlled portion of the clinical trials was greatest in subjects with RA, both in the number of subjects treated and the total subject-years of follow-up. The majority of subjects received either 50 or 100 mg golimumab administered SC, with the total number of subjects treated and the total exposure greater for 100 mg than 50 mg. There

were more female subjects than male subjects in these golimumab clinical trials and the majority of subjects were white. In addition, the majority of subjects were between 18 and 64 years of age.

Table SIII.1: Summary of Subject-years of Follow-up During the Controlled Portions of All Clinical Trials by Golimumab Exposure

	Subjects Treated	Total Subject-years of Follow-up
All trials[a]		
Subjects treated with golimumab	4560	2110
Duration of golimumab exposure		
≥ 16 weeks	3301	1899
≥ 24 weeks	2530	1563

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T29, C0524T08, C0524T09, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, and C0524T17.

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Table SIII.2: Summary of Subject-years of Follow-up During the Controlled Portions of Clinical Trials by Golimumab Exposure

	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]		
Subjects treated with golimumab	1355	840
Duration of golimumab exposure		
≥ 16 weeks	1279	819
≥ 24 weeks	1045	721
RA IV trials[b]		
Subjects treated with golimumab	908	414
Duration of golimumab exposure		
≥ 16 weeks	859	397
≥ 24 weeks	718	334
PsA SC trial (C0524T08)		
Subjects treated with golimumab	292	134
Duration of golimumab exposure		
≥ 16 weeks	282	131
≥ 24 weeks	253	118
PsA IV trial (CNTO148PSA3001)		
Subjects treated with golimumab	240	110
Duration of golimumab exposure		
≥ 16 weeks	229	106
≥ 24 weeks	0	0
AS SC trials[c]		
Subjects treated with golimumab	386	177
Duration of golimumab exposure		
≥ 16 weeks	372	172
≥ 24 weeks	330	154
AS IV trial (CNTO148AKS3001)[d]		
Subjects treated with golimumab	105	32
Duration of golimumab exposure		
≥ 16 weeks	0	0
nrAxSpA SC trial (P07642)		
Subjects treated with golimumab	97	30
Duration of golimumab exposure		
≥ 16 weeks	76	24
Asthma SC trial (C0524T03)		
Subjects treated with golimumab	230	261
Duration of golimumab exposure		
≥ 16 weeks	204	250
≥ 24 weeks	184	238

[a] C0524T02, C0524T05, C0524T06, C0524T11, and C0524T28.
[b] C0524T12 and CNTO148ART3001.
[c] C0524T09 and C0524T29.
[d] The controlled period for CNTO148AKS3001 is through Week 16; the scheduled doses are at Weeks 0, 4, and 12.

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Table SIII.3: Summary of Subject-years of Follow-up During the Controlled Portions of UC Clinical Trials by Golimumab Exposure

	Subjects Treated	Total Subject-years of Follow-up
UC trials[a]		
Subjects treated with golimumab	947	111
IV induction trial (C0524T16)		
Subjects treated with golimumab[b]	213	25
SC induction trial (C0524T17)		
Subjects treated with golimumab[c]	734	86

[a] C0524T16 and C0524T17.
[b] Represents subjects who received the single IV administration of golimumab in C0524T16.
[c] Represents subjects who received at least one of the 2 scheduled SC administrations of golimumab at Week 0 and Week 2 in the C0524T17 trial.

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Table SIII.4: Summary of Subject-years of Follow-up During the Controlled Portions of All Clinical Trials by Age and Sex

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
All trials[a]				
Subjects treated with golimumab	1824	734	2736	1376
Age (yrs)				
18 to 64	1696	678	2486	1242
65 to 74	109	47	216	115
≥ 75	19	9	34	19

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08, C0524T09, C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, and C0524T17.

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Table SIII.5: Summary of Subject-years of Follow-up During the Controlled Portions of Clinical Trials by Age and Sex

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]				
Subjects treated with golimumab	268	158	1087	682
Age (yrs)				
18 to 64	228	138	957	609
65 to 74	31	16	113	63
≥ 75	9	5	17	10
RA IV trials[b]				
Subjects treated with golimumab	169	76	739	338
Age (yrs)				
18 to 64	144	65	661	303
65 to 74	23	10	68	30
≥ 75	2	1	10	4
PsA SC trial (C0524T08)				
Subjects treated with golimumab	175	81	117	54
Age (yrs)				
18 to 64	163	75	113	52
65 to 74	10	4	4	2
≥ 75	2	1	0	0
PsA IV trial (CNTO148PSA3001)				
Subjects treated with golimumab	127	58	113	52
Age (yrs)				
18 to 64	122	55	105	49
65 to 74	5	2	8	4
≥ 75	0	0	0	0
AS SC trials[c]				
Subjects treated with golimumab	290	134	96	43
Age (yrs)				
18 to 64	284	131	93	42
65 to 74	4	2	3	1
≥ 75	2	1	0	0
AS IV trial (CNTO148AKS3001)				
Subjects treated with golimumab	86	27	19	6
Age (yrs)				
18 to 64	86	27	19	6
65 to 74	0	0	0	0
≥ 75	0	0	0	0
nrAxSpA SC trial (P07642)				
Subjects treated with golimumab	61	19	36	11
Age (yrs)				
18 to 64	61	19	36	11
65 to 74	0	0	0	0
≥ 75	0	0	0	0
Asthma SC trial (C0524T03)				
Subjects treated with golimumab	100	118	130	144
Age (yrs)				
18 to 64	88	107	115	126
65 to 74	11	10	11	14
≥ 75	1	1	4	4

[a] C0524T02, C0524T05, C0524T06, C0524T11, and C0524T28.
[b] C0524T12 and CNTO148ART3001.
[c] C0524T09 and C0524T29.

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Table SIII.6: Summary of Subject-years of Follow-up During the Controlled Portions of UC Clinical Trials by Age and Sex

	Male		Female	
	Subjects Treated[b]	Total Subject-years of Follow-up	Subjects Treated[b]	Total Subject-years of Follow-up
UC trials[a]				
Subjects treated with golimumab	548	64	399	47
Age (yrs)				
18 to 64	520	61	387	45
65 to 74	25	3	9	1
≥ 75	3	0	3	0

[a] C0524T16 and C0524T17.
[b] Subjects who received at least one administration of golimumab in C0524T16 or C0524T17.

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Table SIII.7: Summary of Subject-years of Follow-up During the Controlled Portions of All Clinical Trials by Dose Level

	Subjects Treated	Total Subject-years of Follow-up
All trials[a,b,c]		
Subjects treated with golimumab	4560	2109
1 mg/kg	63	7
2 mg/kg	1072	449
4 mg/kg	331	125
50 mg	1162	638
100 mg	1120	714
200 mg	78	91
100 mg at Week 0 and 50 mg at Week 2	71	8
200 mg at Week 0 and 100 mg at Week 2	331	39
400 mg at Week 0 and 200 mg at Week 2	332	38

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08, C0524T09, C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, and C0524T17.
[b] In trial C0524T03, loading dose is 1.5 times the randomized dose of either 50 mg, 100 mg or 200 mg.
[c] Subjects are counted in only one dose group.

[TSFEXPPC02C.rtf] [CNTO148\Z_ADHOC_REQ\DBR_AKSPSA_2016\RE_RMP_CANADA\tsfexppc02c.sas] 22MAY2017, 16:51

Table SIII.8: Summary of Subject-years of Follow-up During the Controlled Portions of Clinical Trials by Dose Level

	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]		
Subjects treated with golimumab	1355	840
50 mg	597	327
100 mg	758	496
RA IV trials[b]		
Subjects treated with golimumab	908	414
2 mg/kg q8 weeks	395	180
2 mg/kg q12 weeks	258	117
4 mg/kg q12 weeks	255	116
PsA SC trial (C0524T08)		
Subjects treated with golimumab	292	134
50 mg	146	62
100 mg	146	68
PsA IV trial (CNTO148PSA3001)		
Subjects treated with golimumab	240	110
2 mg/kg q8 weeks	240	110
AS SC trials[c]		
Subjects treated with golimumab	386	177
50 mg	246	108
100 mg	140	65
AS IV trial (CNTO148AKS3001)		
Subjects treated with golimumab	105	32
2 mg/kg q8 weeks	105	32
nrAxSpA SC trial(P07642)		
Subjects treated with golimumab	97	30
50 mg	97	30
Asthma SC trial (C0524T03)[d]		
Subjects treated with golimumab	230	261
50 mg	76	85
100 mg	76	86
200 mg	78	91

[a] C0524T02, C0524T05, C0524T06, C0524T11, and C0524T28.
[b] C0524T12 and CNTO148ART3001.
[c] C0524T09 and C0524T29.
[d] Loading dose=1.5 times dose shown for asthma trial.

[TSFEXPPC02A.rtf] [CNTO148\Z_ADHOC_REQ\DBR_AKSPSA_2016\RE_RMP_CANADA\tsfexppc02a.sas] 16MAY2017, 18:39

Table SIII.9: Summary of Subject-years of Follow-up During the Controlled Portions of UC Clinical Trials by Dose Level

	Subjects Treated	Total Subject-years of Follow-up
IV induction trial (C0524T16)[a]		
Subjects treated with golimumab	213	25
1 mg/kg at Week 0	63	7
2 mg/kg at Week 0	74	9
4 mg/kg at Week 0	76	9
SC induction trial (C0524T17)[b]		
Subjects treated with golimumab	734	85
100 mg at Week 0 and 50 mg at Week 2	71	8
200 mg at Week 0 and 100 mg at Week 2	331	39
400 mg at Week 0 and 200 mg at Week 2	332	38

[a] The number of subjects treated for each dose level is the number of subjects who received the single IV administration of golimumab at that dose level.
[b] The number of subjects treated for each dose level is the number of subjects who received at least 1 of the 2 scheduled SC administrations of golimumab at Week 0 and Week 2 at that dose level.

[TSFEXPPC02B.rtf] [CNTO148\Z_RMP\DBR_AXSPA_08MAY2014\RE_AXSPA_08MAY2014\tsfexppc02b.sas] 05AUG2014, 09:26

Table SIII.10: Summary of Subject-years of Follow-up During the Controlled Portions of All Clinical Trials by Ethnic Origin

	Subjects Treated	Total Subject-years of Follow-up
All trials[a]		
Subjects treated with golimumab	4560	2110
Ethnic origin		
White	3549	1630
Black	81	45
Asian	654	304
Other	276	130

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08, C0524T09, C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, and C0524T17.

[TSFEXPPC04C.rtf] [CNTO148\Z_ADHOC_REQ\DBR_AKSPSA_2016\RE_RMP_CANADA\tsfexppc04c.sas] 16MAY2017, 18:43

Table SIII.11: Summary of Subject-years of Follow-up During the Controlled Portions of Clinical Trials by Ethnic Origin

	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]		
Subjects treated with golimumab	1355	840
Ethnic origin		
White	973	607
Black	30	14
Asian	277	171
Other	75	49
RA IV trials[b]		
Subjects treated with golimumab	908	414
Ethnic origin		
White	670	305
Black	9	4
Asian	73	33
Other	156	71
PsA SC trial (C0524T08)		
Subjects treated with golimumab	292	134
Ethnic origin		
White	283	130
Black	1	0
Asian	6	3
Other	2	1
PsA IV trial (CNTO148PSA3001)		
Subjects treated with golimumab	240	110
Ethnic origin		
White	240	110
Black	0	0
Asian	0	0
Other	0	0
AS SC trials[c]		
Subjects treated with golimumab	386	177
Ethnic origin		
White	205	94
Black	2	1
Asian	175	80
Other	4	2
AS IV trial (CNTO148AKS3001)		
Subjects treated with golimumab	105	32
Ethnic origin		
White	89	27
Black	0	0
Asian	11	3
Other	5	2
nrAxSpA SC trial (P07642)		
Subjects treated with golimumab	97	30
Ethnic origin		
White	97	30
Black	0	0
Asian	0	0
Other	0	0
Asthma SC trial (C0524T03)		
Subjects treated with golimumab	230	261
Ethnic origin		
White	205	235
Black	21	23
Asian	1	1
Other	3	2

[a] C0524T02, C0524T05, C0524T06, C0524T11, and C0524T28.
[b] C0524T12 and CNTO148ART3001.
[c] C0524T09 and C0524T29.

[TSFEXPPC04A.rtf] [CNTO148\Z_ADHOC_REQ\DBR_AKSPSA_2016\RE_RMP_CANADA\tsfexppc04a.sas] 16MAY2017, 18:42

Table SIII.12: Summary of Subject-years of Follow-up During the Controlled Portions of UC Clinical Trials by Ethnic Origin

	Subjects Treated	Total Subject-years of Follow-up
UC trials[a]		
Subjects treated with golimumab	947	111
Ethnic origin		
White	787	92
Black	18	2
Asian	111	13
Other	31	4

[a] C0524T16 and C0524T17.

[TSFEXPPC04B.rtf] [CNTO148\Z_RMP\DBR_AXSPA_08MAY2014\RE_AXSPA_08MAY2014\tsfexppc04b.sas] 05AUG2014, 13:50

Exposure Through the End of the Reporting Period

Data from the following completed trials in adults and children are included in the tables describing exposure through the end of the reporting period (ie, all portions of clinical trials, including open-label extensions):

- SC/IV Phase 2 and 3 trials in the rheumatologic indications (RA, PsA, AS, and nr-AxSpA: C0524T02, C0524T05, C0524T06, C0524T11, C0524T12 [SC portion only in the long-term extension of trial], CNTO148ART3001, C0524T28, C0524T08, C0524T09, C0524T29, P07642, CNTO148PSA3001, and CNTO148AKS3001).
- SC Phase 2b trial in asthma (C0524T03)
- SC/IV Phase 2/3 trials in UC (C0524T16, C0524T17, and C0524T18)
- SC Phase 3 trial in pJIA (CNTO148JIA3001)

A total of 6,381 subjects were exposed to golimumab in adult trials (Tables SIII.13, SIII.17, SIII.21, and SIII.25). A total of 173 subjects were exposed to golimumab in the pediatric pJIA trial (Tables SIII.16, SIII.20, SIII.24, and SIII.28).

Rheumatoid arthritis was the indication with the greatest exposure to golimumab through the end of the reporting period, both in the number of subjects treated and the total subject-years of follow-up. The majority of subjects received either 50 or 100 mg golimumab administered SC with total exposure greater for 100 mg than for 50 mg. As seen in the controlled portion of these clinical trials, there were more female subjects than male subjects through the end of the reporting period and the majority of subjects were white. In addition, through the end of the reporting period, the majority of subjects were between 18 and 64 years of age.

Table SIII.13: Summary of Subject-years of Follow-up in All Trials Through the End of the Reporting Period by Golimumab Exposure; Treated Subjects in All Trials

	Subjects Treated	Total Subject-years of Follow-up
All trials[a]		
Subjects treated with golimumab	6381	15321
Duration of golimumab exposure		
≥ 16 weeks	5786	15018
≥ 24 weeks	5577	14892
≥ 52 weeks	3973	13406
≥ 104 weeks	2343	10554
≥ 160 weeks	2026	9696
≥ 208 weeks	1779	8727

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08, C0524T09, C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, C0524T17, and C0524T18.

[TSFEXPRP01C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\tsfexprp01c.sas] 19JAN2018, 12:21

Table SIII.14: Summary of Subject-years of Follow-up Through the End of the Reporting Period by Golimumab Exposure; Treated Subjects in Rheumatologic and Asthma Trials

	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]		
Subjects treated with golimumab	2385	6362
Duration of golimumab exposure		
≥ 16 weeks	2270	6325
≥ 24 weeks	2208	6291
≥ 52 weeks	1241	5451
≥ 104 weeks	1112	5223
≥ 160 weeks	1014	4938
≥ 208 weeks	866	4350
RA IV trials[b]		
Subjects treated with golimumab	1210	1840
Duration of golimumab exposure		
≥ 16 weeks	1172	1830
≥ 24 weeks	1161	1824
≥ 52 weeks	999	1695
≥ 100 weeks	300	647
PsA SC trial (C0524T08)		
Subjects treated with golimumab	394	1648
Duration of golimumab exposure		
≥ 16 weeks	379	1642
≥ 24 weeks	374	1640
≥ 52 weeks	353	1622
≥ 104 weeks	332	1586
≥ 160 weeks	313	1536
≥ 208 weeks	294	1464
PsA IV trial (CNTO148PSA3001)		
Subjects treated with golimumab	460	417
Duration of golimumab exposure		
≥ 16 weeks	446	412
≥ 24 weeks	437	407
≥ 52 weeks	192	223
AS SC trials[c]		
Subjects treated with golimumab	564	1644
Duration of golimumab exposure		
≥ 16 weeks	545	1638
≥ 24 weeks	526	1626
≥ 52 weeks	312	1432
≥ 104 weeks	286	1391
≥ 160 weeks	276	1363
≥ 208 weeks	264	1317
AS IV trial (CNTO148AKS3001)		
Subjects treated with golimumab	204	203
Duration of golimumab exposure		
≥ 16 weeks	201	202
≥ 24 weeks	198	199
≥ 52 weeks	85	99
nrAxSpA SC trial (P07642)		
Subjects treated with golimumab	193	185
Duration of golimumab exposure		
≥ 16 weeks	184	182
≥ 24 weeks	183	181
Asthma SC trial (C0524T03)		
Subjects treated with golimumab	231	261
Duration of golimumab exposure		
≥ 16 weeks	204	250
≥ 24 weeks	184	238
≥ 52 weeks	93	134

[a] C0524T02, C0524T05, C0524T06, C0524T11, C0524T28, and C0524T12 (SC portion only in the LTE of trial).
[b] C0524T12 (through Week 48 database lock which includes only IV portion of the trial) and CNTO148ART3001.
[c] C0524T09 and C0524T29.

[TSFEXPRP01A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\tsfexprp01a.sas] 01FEB2018, 02:26

Table SIII.15: Summary of Subject-years of Follow-up in UC Clinical Trials Through the End of the Reporting Period by Golimumab Exposure; Treated Subjects in the UC Trials

	Subjects Treated	Total Subject-years of Follow-up
UC trials[a]		
Subjects treated with golimumab[b]	1245	2760
Duration of golimumab exposure[c]		
≥ 6 weeks	1049	2611
≥ 30 weeks	769	2455
≥ 58 weeks	621	2297
≥ 110 weeks	498	2072

[a] C0524T16, C0524T17, and C0524T18.
[b] Includes subjects who received a single IV administration of golimumab in C0524T16, at least one of the 2 SC administrations of golimumab in C0524T17, or at least one SC administration of golimumab in C0524T18.
[c] Cumulative exposure of golimumab over the 6-week dosing interval in induction (C0524T16 or C0524T17) and the dosing interval during the main and extension portion of the maintenance trial (C0524T18).

[TSFEXPRP01B.rtf] [CNTO148\Z_RMP\DBR_AXSPA_T18_FINAL\RE_AXSPA_T18_FINAL\tsfexprp01b.sas] 11OCT2015, 20:57

Table SIII.16: Summary of Subject-years of Follow-up Through the End of the Reporting Period in pJIA SC Trial by Golimumab Exposure

	Subjects Treated	Total Subject-years of Follow-up
pJIA SC trial(CNTO148JIA3001)		
Subjects treated with golimumab	173	326
Duration of golimumab exposure		
≥ 16 weeks	144	301
≥ 48 weeks	134	292

[TSFEXPRP01.rtf] [CNTO148\JIA3001\DBR_FINAL\RE_RMP\tsfexprp01.sas] 29JUN2015, 16:57

Table SIII.17: Summary of Subject-years of Follow-up in All Clinical Trials Through the End of the Reporting Period by Age and Sex; Treated Subjects in All Trials

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
All trials[a]				
Subjects treated with golimumab	2579	5976	3802	9344
Age (yrs)				
18 to 64	2419	5604	3462	8517
65 to 74	136	312	290	693
≥ 75	24	61	50	135

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08, C0524T09, C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, C0524T17, and C0524T18.

[TSFEXPRP03C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\tsfexprp03c.sas] 19JAN2018, 12:24

Table SIII.18: Summary of Subject-years of Follow-up Through the End of the Reporting Period by Age and Sex; Treated Subjects in Rheumatologic and Asthma Trials

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]				
Subjects treated with golimumab	459	1216	1926	5146
Age (yrs)				
18 to 64	392	1053	1720	4590
65 to 74	54	124	173	450
≥ 75	13	40	33	106
RA IV trials[b]				
Subjects treated with golimumab	230	339	980	1501
Age (yrs)				
18 to 64	201	298	879	1342
65 to 74	27	38	90	144
≥ 75	2	2	11	16
PsA SC trial (C0524T08)				
Subjects treated with golimumab	236	980	158	668
Age (yrs)				
18 to 64	222	929	151	638
65 to 74	12	47	7	29
≥ 75	2	4	0	0
PsA IV trial (CNTO148PSA3001)				
Subjects treated with golimumab	236	215	224	202
Age (yrs)				
18 to 64	224	206	207	186
65 to 74	11	9	16	15
≥ 75	1	1	1	1
AS SC trials[c]				
Subjects treated with golimumab	430	1235	134	409
Age (yrs)				
18 to 64	424	1216	130	393
65 to 74	4	13	4	16
≥ 75	2	6	0	0
AS IV trial (CNTO148AKS3001)				
Subjects treated with golimumab	161	163	43	40
Age (yrs)				
18 to 64	161	163	43	40
65 to 74	0	0	0	0
≥ 75	0	0	0	0
nrAxSpA SC trial (P07642)				
Subjects treated with golimumab	111	109	82	76
Age (yrs)				
18 to 64	111	109	82	76
65 to 74	0	0	0	0
≥ 75	0	0	0	0
Asthma SC trial (C0524T03)				
Subjects treated with golimumab	100	118	131	144
Age (yrs)				
18 to 64	88	107	116	126
65 to 74	11	10	11	14
≥ 75	1	1	4	4

[a] C0524T02, C0524T05, C0524T06, C0524T11, C0524T28, and C0524T12 (SC portion only in the LTE of trial).
[b] C0524T12 (through Week 48 database lock which includes only IV portion of the trial) and CNTO148ART3001.
[c] C0524T09 and C0524T29.

[TSFEXPRP03A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\tsfexprp03a.sas] 01FEB2018, 02:25

Table SIII.19 Summary of Subject-years of Follow-up in UC Clinical Trials Through the End of the Reporting Period by Age and Sex; Treated Subjects in the UC Trials

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
UC trials[a]				
Subjects treated with golimumab	712	1601	533	1159
Age (yrs)				
18 to 64	677	1523	517	1125
65 to 74	32	71	13	25
≥ 75	3	7	3	8

[a] C0524T16, C0524T17, and C0524T18.

[TSFEXPRP03B.rtf] [CNTO148\Z_RMP\DBR_AXSPA_T18_FINAL\RE_AXSPA_T18_FINAL\tsfexprp03b.sas] 11OCT2015, 20:58

Table SIII.20: Summary of Subject-years of Follow-up Through the End of the Reporting Period in pJIA SC Trial by Age and Sex

	Male		Female	
	Subjects Treated	Total Subject-years of Follow-up	Subjects Treated	Total Subject-years of Follow-up
pJIA SC trial (CNTO148JIA3001)				
Subjects treated with golimumab	42	79	131	247
Age (yrs)				
2 to 11	18	36	65	122
≥ 12	24	43	66	125

[TSFEXPRP03.rtf] [CNTO148\JIA3001\DBR_FINAL\RE_RMP\tsfexprp03.sas] 29JUN2015, 16:57

Table SIII.21: Summary of Subject-years of Follow-up in All Trials Through the End of the Reporting Period by Dose Level; Treated Subjects in All Trials

	Subjects Treated	Total Subject-years of Follow-up
All trials[a,b,c]		
Subjects treated with golimumab	6381	15321
1 mg/kg	63	8
2 mg/kg	1581	1990
4 mg/kg	493	490
50 mg	2722	4686
100 mg	2694	7765
200 mg	102	144
100 mg at Week 0 and 50 mg at Week 2[d]	71	9
200 mg at Week 0 and 100 mg at Week 2[d]	331	41
400 mg at Week 0 and 200 mg at Week 2[d]	332	43

[a]C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08 , C0524T09, C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16 and C0524T17 include follow-up for induction phase only, and C0524T18.
[b] In trial C0524T03, first/loading dose was 1.5 times the randomized dose of either 50 mg, 100 mg or 200 mg.
[c] Due to dose changes in some trials, subjects may be counted in more than one dose group.
[d] Subjects from trial C0524T17 are not counted in the individual dose groups of 50 mg, 100 mg, and 200 mg.

[TSFEXPRP02C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\tsfexprp02c.sas] 19JAN2018, 12:21

Table SIII.22: Summary of Subject-years of Follow-up Through the End of the Reporting Period by Dose Level; Treated Subjects in Rheumatologic and Asthma Trials

	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]		
Subjects treated with golimumab	2385	6362
50 mg[b]	1625	2465
100 mg	1175	3904
RA IV trials[c]		
Subjects treated with golimumab	1210	1840
2 mg/kg q8 weeks	584	1077
2 mg/kg q12 weeks	259	282
4 mg/kg q12 weeks	417	481
PsA SC trial (C0524T08)		
Subjects treated with golimumab	394	1648
50 mg	248	672
100 mg	255	979
PsA IV trial (CNTO148PSA3001)		
Subjects treated with golimumab	460	417
2 mg/kg q8 weeks	460	417
AS SC trials[d]		
Subjects treated with golimumab	564	1644
50 mg	424	904
100 mg	195	743
AS IV trial (CNTO148AKS3001)		
Subjects treated with golimumab	204	203
2 mg/kg q8 weeks	204	203
nrAxSpA SC trial (P07642)		
Subjects treated with golimumab	193	185
50 mg	193	185
Asthma SC trial (C0524T03)[e]		
Subjects treated with golimumab	231	261
50 mg	77	85
100 mg	76	86
200 mg	78	91

[a] C0524T02, C0524T05, C0524T06, C0524T11, C0524T28, and C0524T12 (SC portion only in the LTE of trial).
[b] Includes subjects from C0524T12 who switched from IV to SC administrations.
[c] C0524T12 (through Week 48 database lock which includes only IV portion of the trial) and CNTO148ART3001.
[d] C0524T09 and C0524T29.
[e] Loading dose=1.5 times dose shown for asthma trial.

[TSFEXPRP02A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\tsfexprp02a.sas] 01FEB2018, 02:27

Table SIII.23: Summary of Subject-years of Follow-up in UC Clinical Trials Through the End of the Reporting Period by Dose Level; Treated Subjects in the UC Trials

	Subjects Treated	Total Subject-years of Follow-up
UC trials[a]		
Subjects treated with golimumab	1245	2760
IV induction (C0524T16)[b]		
1 mg/kg at Week 0	63	8
2 mg/kg at Week 0	74	10
4 mg/kg at Week 0	76	9
SC induction (C0524T17)[c]		
100 mg at Week 0 and 50 mg at Week 2	71	9
200 mg at Week 0 and 100 mg at Week 2	331	41
400 mg at Week 0 and 200 mg at Week 2	332	43
SC maintenance (C0524T18)[d]		
50 mg	155	376
100 mg	993	2052
200 mg	24	53

[a] C0524T16 and C0524T17 include follow-up for induction phase only, and C0524T18.
[b] The number of subjects treated for each dose level is the number of subjects who received the single IV administration of golimumab at that dose level.
[c] The number of subjects treated for each dose level is the number of subjects who received at least one of the 2 scheduled SC administrations of golimumab at Week 0 and Week 2 at that dose level.
[d] The number of subjects treated for each dose level is the number of subjects who received at least one SC administration of golimumab at that dose level. Due to dose adjustment, subjects may be counted in more than 1 dose group.

[TSFEXPRP02B.rtf] [CNTO148\Z_RMP\DBR_AXSPA_T18_FINAL\RE_AXSPA_T18_FINAL\tsfexprp02b.sas] 16OCT2015, 08:41

Table SIII.24: Summary of Subject-years of Follow-up Through the End of the Reporting Period in pJIA SC Trial by Dose Level

	Subjects Treated	Total Subject-years of Follow-up
pJIA SC trial(CNTO148JIA3001)		
Subjects treated with golimumab	173	326
30 mg/m^2	173	326

[TSFEXPRP02.rtf] [CNTO148\JIA3001\DBR_FINAL\RE_RMP\tsfexprp02.sas] 29JUN2015, 16:57

Table SIII.25: Summary of Subject-years of Follow-up in All Clinical Trials Through the End of the Reporting Period by Ethnic Origin; Treated Subjects in All Trials

	Subjects Treated	Total Subject-years of Follow-up
All trials[a]		
Subjects treated with golimumab	6381	15321
Ethnic origin		
White	4889	12197
Black	104	210
Asian	1024	2044
Other	364	870

[a] C0524T02, C0524T03, C0524T05, C0524T06, C0524T11, C0524T28, C0524T08, C0524T09 , C0524T29, P07642, C0524T12, CNTO148ART3001, CNTO148PSA3001, CNTO148AKS3001, C0524T16, C0524T17, and C0524T18.

[TSFEXPRP04C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\Tsfexprp04c.sas] 29JAN2018, 12:45

Table SIII.26: Summary of Subject-years of Follow-up Through the End of the Reporting Period by Ethnic Origin; Treated Subjects in Rheumatologic and Asthma Trials

	Subjects Treated	Total Subject-years of Follow-up
RA SC trials[a]		
Subjects treated with golimumab	2385	6362
Ethnic origin		
White	1631	4818
Black	48	98
Asian	495	991
Other	211	455
RA IV trials[b]		
Subjects treated with golimumab	1210	1840
Ethnic origin		
White	908	1406
Black	13	17
Asian	93	137
Other	196	281
PsA SC trial (C0524T08)		
Subjects treated with golimumab	394	1648
Ethnic origin		
White	382	1596
Black	2	10
Asian	7	31
Other	3	11
PsA IV trial (CNTO148PSA3001)		
Subjects treated with golimumab	460	417
Ethnic origin		
White	459	417
Black	0	0
Asian	1	1
Other	0	0
AS SC trials[c]		
Subjects treated with golimumab	564	1644
Ethnic origin		
White	259	1020
Black	3	15
Asian	296	593
Other	6	16
AS IV trial (CNTO148AKS3001)		
Subjects treated with golimumab	204	203
Ethnic origin		
White	176	175
Black	0	0
Asian	19	20
Other	9	9
nrAxSpA SC trial (P07642)		
Subjects treated with golimumab	193	185
Ethnic origin		
White	193	185
Black	0	0
Asian	0	0
Other	0	0
Asthma SC trial (C0524T03)		
Subjects treated with golimumab	231	261
Ethnic origin		
White	206	235
Black	21	23
Asian	1	1
Other	3	2

[a] C0524T02, C0524T05, C0524T06, C0524T11, C0524T28, and C0524T12 (SC portion only in the LTE of trial).
[b] C0524T12 (through Week 48 database lock which includes only IV portion of the trial) and CNTO148ART3001.
[c] C0524T09 and C0524T29.

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Table SIII.27: Summary of Subject-years of Follow-up in UC Clinical Trials Through the End of the Reporting Period by Ethnic Origin; Treated Subjects in the UC trials

	Subjects Treated	Total Subject-years of Follow-up
UC trials[a]		
Subjects treated with golimumab	1245	2760
Ethnic origin		
White	1026	2345
Black	24	48
Asian	155	271
Other	40	96

[a] C0524T16, C0524T17, and C0524T18.

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Table SIII.28: Summary of Subject-years of Follow-up Through the End of the Reporting Period in pJIA SC Trial by Ethnic Origin

	Subjects Treated	Total Subject-years of Follow-up
pJIA SC trial(CNTO148JIA3001)		
Subjects treated with golimumab	173	326
Ethnic origin		
White	152	286
Black	2	5
Asian	0	-
Other	19	35

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Trials Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Had a known hypersensitivity to human Ig proteins or other components of golimumab.	
Reason for being an exclusion criterion	Individuals with a known hypersensitivity to human IgG proteins or any of the components of golimumab would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	SIMPONI is contraindicated in patients with a history of hypersensitivity to golimumab or to any of the excipients (SmPC, section 4.3).

Had an active infection:

- **Active granulomatous infection, including tuberculosis, histoplasmosis, or coccidioidomycosis.**
- **Current active infection, including tuberculosis.**
- **Nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, *Pneumocystis carinii*, aspergillosis) within 6 months prior to the start of treatment with golimumab.**
- **Serious infection (eg, hepatitis, pneumonia, pyelonephritis, sepsis), or hospitalized for an infection, or treated with IV antibiotics for an infection within 2 months prior to the start of treatment with golimumab.**
- **Ongoing chronic recurrent infectious disease.**

Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection. Serious infections are considered a class effect of these agents.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Serious infections is an important identified risk. Information about infections is described in the SmPC. The risk to this patient population is adequately addressed in the SmPC and the Patient Reminder Card.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Had a history of, or concurrent, congestive heart failure, including medically controlled, asymptomatic congestive heart failure.	
Reason for being an exclusion criterion	In a clinical trial with another TNF-antagonist, worsening congestive heart failure (CHF) and increased mortality due to CHF have been observed.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Moderate or severe heart failure (New York Heart Association [NYHA] class III/IV) is a contraindication in the SmPC. The risk to this patient population is adequately addressed in the SmPC.
Had a history of latent granulomatous infection including tuberculosis (exception C0524T11), histoplasmosis, or coccidioidomycosis.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Serious infections is an important identified risk. Information about infections, including tuberculosis (TB), is described in the SmPC. The risk to this patient population is adequately addressed in the SmPC and the Patient Reminder Card.
Were known to be infected with HIV, hepatitis B, or hepatitis C.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection. In addition, the use of anti-TNFα agents has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of the virus.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Serious infections is an important identified risk. Information about infections, including hepatitis B, is described in the SmPC. The risk to this patient population is adequately addressed in the SmPC and the Patient Reminder Card.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Had a history of chronic or recurrent infectious disease.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Section 4.4 of the SmPC states that caution should be exercised when considering the use of SIMPONI in patients with a chronic infection or a history or recurrent infection.
Had current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease.	
Reason for being an exclusion criterion	This is a typical, prudent, precautionary position applied to clinical trial subjects when a drug was not widely used in humans.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	The impracticalities of identifying adequate numbers of patients with similar progressive concomitant disease in each of these categories precludes the further study of SIMPONI in these patient populations. These components are therefore not considered appropriate for further study under the category of missing information. Given the severity of disease in subjects with severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, the risk/benefit balance of the use of SIMPONI should be carefully evaluated on a case-by-case basis. Guidance on the use of SIMPONI in subjects with hematologic and neurologic disorders is provided in section 4.4 of the SmPC (Special warnings and precautions for use).
Had a history of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location, or clinically significant splenomegaly.	
Reason for being an exclusion criterion	Use of anti-TNFα agents has been associated with the occurrence of lymphoma.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Malignancy is an important identified risk. The risk of lymphoma in this patient population is adequately addressed in the SmPC.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Had any known malignancy or had a history of malignancy within the previous 5 years (with the exception of a nonmelanoma skin cancer that had been treated with no evidence of recurrence).	
Reason for being an exclusion criterion	Published medical literature suggests that certain types of malignancies may be adversely affected by TNFα blockade. The potential role of TNF-blocking therapy in the development of certain types of malignancies is not known.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Malignancy is an important identified risk. The risk to this patient population is adequately addressed in the SmPC.
Had received or were expected to receive any live virus or bacterial vaccination (including Bacille Calmette-Guérin) within 3 to 12 months before the first administration of the study agent/screening, during the trial, or within 6 months after the last administration.	
Reason for being an exclusion criterion	Treatment with anti-TNFα agents may increase the risk of the development of infections or worsen an existing infection.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero is an important potential risk. The risk of live vaccinations is adequately addressed in the SmPC and the Patient Reminder Card.
History of known demyelinating diseases such as multiple sclerosis or optic neuritis.	
Reason for being an exclusion criterion	Anti-TNFα agents have been associated with demyelinating diseases (central and peripheral) and these events are considered a class effect for these agents.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	Demyelinating disorders is an important identified risk. The risk to this patient population is adequately addressed in the SmPC.
Had previously used any biologics (eg, infliximab, etanercept, adalimumab, rituximab, natalizumab) as specified in the protocol.	
Reason for being an exclusion criterion	These agents were prohibited or required a washout period to reduce the risk of concomitant immunosuppression or the risk of adverse events (AEs) after the use of these agents.
Considered to be included as missing information?	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Rationale (if not included as missing information)	This risk is adequately addressed in the SmPC.
Had used cytotoxic agents, including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents.	
Reason for being an exclusion criterion	To reduce the risk of concomitant immunosuppressants or the risk of AEs after cytotoxic agent use, these agents were prohibited or required a washout period.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	The concomitant use of biologics and other immunosuppressants for the treatment of autoimmune disease is associated with an increase in AEs with no increase in efficacy (Genovese 2004; Weinblatt 2006). The risk of immunosuppression with SIMPONI and interactions with other medicinal products is addressed in the SmPC (section 4.4).
Pregnant, nursing, or planning a pregnancy or fathering a child within 6 months after receiving the last administration of trial medication.	
Reason for being an exclusion criterion	Per International Council on Harmonisation (ICH) guidelines, pregnant women should normally be excluded from clinical trials.
Considered to be included as missing information?	No
Rationale (if not included as missing information)	<u>Exposure during pregnancy</u> Guidance for the use of SIMPONI during pregnancy is provided in the SmPC (section 4.6). Neither routine nor additional pharmacovigilance activities have identified any safety signals associated with the use of SIMPONI during pregnancy. The MAH considers that sufficient exposure data have been collected and no longer considers exposure during pregnancy as missing information. <u>Use during breastfeeding</u> Guidance for the use of SIMPONI during breastfeeding is provided in the SmPC (section 4.6).
Had a transplanted organ (with the exception of a corneal transplant performed >3 months prior to first administration of trial medication).	
Reason for being an exclusion criterion	The risk of concomitant major immunosuppression was unclear at the start of the clinical development program.
Considered to be included as missing information?	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Patients with transplanted organs are generally receiving other immunosuppressants. It would not be appropriate to put these patients at risk by studying the use of SIMPONI in this population.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions due to prolonged exposure, adverse reactions due to cumulative effect, and adverse reactions that have a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women Breastfeeding women	Although prohibited by protocol, exposure to SIMPONI during pregnancy occurred in the clinical development program. A total of 101 cases of exposure to SIMPONI during pregnancy were reported in clinical trials. Breastfeeding women were not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Generally, patients with relevant comorbidities were not included in the clinical development program. However, by default, subjects participating in SIMPONI clinical trials are immunocompromised as a result of their underlying disease, their concomitant medications, and by virtue of receiving treatment with a TNFα inhibitor.
Population with relevant different ethnic origin	SIMPONI clinical trials have been conducted globally in a variety of ethnic groups. The majority of subjects in clinical trials were white.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Children	A total of 173 children aged ≥2 to <18 years of age were exposed to SIMPONI in the completed CNTO148JIA3001 trial in pJIA.

Type of Special Population	Exposure
Elderly	A total of 500 subjects ≥65 years old (160 male and 340 female) have been exposed to SIMPONI in the completed clinical trials. Of these subjects, 74 were ≥75 years old.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Postmarketing Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the times a medication is distributed until it is used by a patient.

Patient Exposure (Person-Time)

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The patient exposure estimates for commercially used drug were calculated using models generated by the Company using insurance claims and hospital discharge data in the US and customized Market Research studies in major markets for outside of the US. These models will be refined over time as usage changes and the companies have come to understand usage better. Estimates of golimumab commercial units sold, patients exposed to golimumab in the current period and a cumulative estimate of patients exposed from launch are presented. For golimumab, each single-use auto-injector or PFS contains 50 mg of golimumab. The recommended dosage for approved indications excluding the UC indication is 50 mg given as a SC injection once a month, on the same date every month. For some patients, the appropriate dosing is 100 mg per month, and the assumption is that 1 unit is equivalent to 1 person-month. The estimate for number of patients exposed in the setting of commercial use includes registries, postmarketing surveillance studies, and epidemiology studies. Cumulative estimates for patients in a specific Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) period are estimated by adding the newly treated patients in that period to the estimate of cumulative patients treated as reported in the previous PBRER/PSUR period after accounting for patients that may have dropped off treatment. This prevents double counting of patients.

SV.1.2. Exposure

The worldwide registered formulations of golimumab are solution for injection for SC administration and solution for IV infusion. The IV formulation of golimumab is not approved in the EU; therefore, this section of the EU-RMP presents postmarketing exposure information for the SC formulation only.

As described in the EU PBRER/PSUR (cut-off date: 06 April 2023), the exposure to commercial golimumab in person-time from launch through 28 February 2023 is 21,649,522 person-months or 1,804,127 person-years.

Table SV.1 below presents the cumulative SC golimumab patient exposure by indication and region from launch.

Table SV.1: Cumulative Golimumab SC Patient Exposure From Launch Through 28 February 2023

Region	Country	RA	PsA	AS	UC	Nr-AxSpa[a]	Other	Total
Canada	Canada	31,386	11,014	18,893	2,790	0	1,909	65,992
EU/N[b]	Austria	12,226	4,439	6,277	946	378	312	24,578
	Baltics (incl. Estonia, Latvia and Lithuania)	489	194	259	39	13	15	1,008
	Belgium/ Luxemburg	8,115	3,137	4,188	610	231	236	16,518
	Bulgaria	1,745	662	934	149	63	52	3,604
	Czech Republic	3,432	1,276	1,788	276	103	105	6,979
	Denmark	4,961	1,917	2,641	391	134	158	10,202
	Finland	6,816	2,453	3,562	542	190	177	13,740
	France	47,257	4,972	27,879	451	0	1,125	81,684
	Germany	38,377	16,600	16,842	6,230	1,940	501	80,489
	Greece/Cyprus	10,367	3,833	5,368	776	282	265	20,892
	Hungary	3,958	1,579	2,038	239	75	107	7,996
	Italy	19,155	12,713	7,018	3,470	1,028	581	43,964
	Malta	1	1	1	0	0	0	2
	Netherlands	6,936	2,675	3,614	490	169	194	14,078
	Norway	6,835	2,739	3,567	458	178	205	13,981
	Poland	2,330	791	1,201	215	68	63	4,667
	Portugal	3,341	1,247	1,755	266	96	95	6,800
	Romania	1,203	402	618	111	54	21	2,409
	Slovakia	2,416	961	1,283	207	68	91	5,026
	Slovenia	948	357	491	72	27	26	1,922
	Spain	17,160	6,487	12,780	1,474	497	972	39,370
	Sweden	7,106	2,755	3,727	593	233	239	14,653
	UK/Ireland	26,438	12,594	10,170	2,078	665	0	51,946
	Croatia	987	399	568	68	26	23	2,071
ROW[b]	Switzerland	12,004	4,493	6,280	920	326	329	24,352
	Israel	3,340	1,274	1,758	262	101	87	6,823
	Mexico	2,221	696	1,164	171	56	33	4,341
	Saudi Arabia	494	234	313	65	10	12	1,128
	All Other*	98,107	32,762	51,725	7,997	1,864	2,253	194,708
US[c]	United States	100,457	23,349	15,558	9,154	0	11,635	160,152
Japan[d]	Japan	178,768	0	0	13,934	0	0	192,701
Total[e,f]		**659,375**	**159,003**	**214,260**	**55,443**	**8,875**	**21,822**	**1,118,777**

*Singapore, Jordan, Australia, Serbia and Montenegro, India, Iran/Yemen/Sudan, Puerto Rico (Bahamas, Barbados, Cayman), Turkey, Bosnia, Russia, Venezuela, Macedonia/Albania/Kosovo, Bahrain, Bolivia, Brazil, Colombia, Ecuador, Egypt, Hong Kong, Ireland, Kazakhstan, Kenya, Kuwait, Lebanon, Malaysia, Muskat Oman, Panama, Paraguay, Peru, Philippines, Qatar, Syria, South Africa, South Korea, Taiwan, Thailand, UAE, Ukraine, Vietnam, Argentina, Chile and Moldova. For PBRERs 1 to 10, Croatia was grouped under ROW. Starting in PBRER 11, Croatia is included under EU, Starting in Period 13, Mexico and Israel are listed separately under ROW.

Key: AS=Ankylosing Spondylitis; EU/N=European Union/Norway; Nr-AxSpa=Non-radiographic Axial Spondyloarthritis; PBRER=Periodic Benefit Risk Evaluation Report; PsA=Psoriatic Arthritis; RA=Rheumatoid Arthritis; ROW=Rest of World; SC=Subcutaneous; UC=Ulcerative Colitis; UK=United Kingdom; UAE=United Arab Emirates; US=United States.

[a] Non-radiographic axial spondyloarthritis was added in Period 15.

[b] In Period 18, EU/N and ROW patient exposure for Period 17 (Apr. 2017 through Sept. 2017) was restated using updated indication-level syringe splits. Restatements were required due to a methodology change in deriving France syringe splits, and to ensure consistency across historical and future periods.

[c] In Period 18, US patient exposure for Period 17 (April 2017 through September 2017) was restated using 2016 IMS claims data, due to inconsistencies in the 2017 claims data.

[d] Product recently launched in Japan, a partner territory. Most patients for Japan are enrolled in Company sponsored studies, this is addressed in the clinical section of the PBRER.

[e] In Period 19, patient exposure for Period 18 (October 2017 through March 2018) was restated with actual unit data.

Table SV.1: Cumulative Golimumab SC Patient Exposure From Launch Through 28 February 2023

Region	Country	RA	PsA	AS	UC	Nr-AxSpa[a]	Other	Total

[f] In Period 21, patient exposure for Period 20 (October 2018 through March 2019) was restated with actual unit data.

Additional Stratifications for Golimumab

Additional stratifications are provided in the PBRER/PSUR using International Marketing Services (IMS) data where possible and appropriate. Prescription units are reported as absolute values.

Exposure by age and gender are presented as a percentage of total prescription sales. Further breakdown by gender within age group are not provided since it is not appropriate to stratify to this level of detail based on prescription information available from IMS for these subcategories.

Table SV.2: Postmarketing (Nonstudy) Golimumab Exposure by Age Group in EU (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	EU[b](157,526 Rx[c])
0 to 17	0.1%
18 to 35	16.3%
36 to 64	67.1%
≥65	16.5%

Key: EU=European Union; Rx=Prescription.
a: Regional Rx data by age were only available for the last 3 years ending December 2019.
b: Data stratified by age were only available in France, Germany, Italy, and United Kingdom.
c: Includes retail channels.

Table SV.3: Postmarketing (Nonstudy) Golimumab Exposure by Age Group Outside EU (01 January 2020 to 31 December 2022)

Age Groups (Years)[a]	Non-EU[b](3,427,106 Rx[c])
0 to 15	0.01%
16 to 35	6.71%
36 to 65	21.60%
≥66	71.68%

Key: EU=European Union; Rx=Prescription.
a: Regional Rx data by age were only available for the last 3 years ending December 2022.
b: Data stratified by age were only available in Japan, and the United States.
c: Includes retail channels.

Table SV.4: Postmarketing (Nonstudy) Golimumab Exposure by Gender (01 January 2020 to 31 December 2022)

Country	Females[a]	Males[a]	Patient Sex Unidentified[a]
Japan (3,312,460 Rx[b])	83.05%	15.37%	1.58%
United States (114,646 Rx[b])	72.92%	27.08%	0.00%

Key: Rx=Prescription.
a: Regional Rx data by gender were only available for the last 3 years ending December 2022. Data were only available for Japan and the United States.
b: Includes retail channels.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

No trials have been conducted to evaluate the dependence potential of golimumab. Drugs with abuse potential generally include drugs that affect the central nervous system, drugs that are chemically or pharmacologically similar to other drugs with known abuse potential, and drugs that produce psychoactive effects such as sedation, euphoria, or mood change (Food and Drug Administration. Assessment of abuse potential of drugs. Guidance for industry).

As a class, therapeutic mAbs are not associated with dependence; their chemical structure differs from central nervous system-active drugs associated with dependence. The pharmaceutical characteristics and pharmacokinetic (PK)/pharmacodynamic (PD) characteristics of golimumab are not characteristic of drugs with high dependence potential (eg, rapid onset/short-acting active substances).

PART II: SAFETY SPECIFICATION

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:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

With the completion of the MK-8259-013 and MK-8259-042 studies, and following a review of available data to date, the important potential risk "Colon cancer/dysplasia (in ulcerative colitis)" and missing information "Long-term safety in adult patients with UC" have been removed from the list of safety concerns.

Rationale for Removal of the Important Potential Risk "Colon carcinoma/dysplasia (in ulcerative colitis)"

- The MK-8259-013 and MK-8259-042 studies are the only remaining additional pharmacovigilance activities in the SIMPONI EU-RMP to address the important potential risk "Colon cancer/dysplasia (in ulcerative colitis)". Long-term data from these studies showed no increased risk of colon carcinoma/dysplasia in UC patients treated with golimumab.

- The results of a cumulative evaluation of data from the Global Medical Safety (GMS) global safety database and the published literature do not support a causal association between golimumab exposure and the development of colon cancer/dysplasia in UC patients.

- Colon cancer/dysplasia will be addressed in the EU-RMP under the more general important identified risk "Malignancy" and will continue to be evaluated in the PSUR.

- Routine pharmacovigilance activities (including the Topic of Interest [TOI] targeted follow-up questionnaire [TFUQ] to collect information on malignancy events) and routine risk minimization measures (as described in Section 4.4 of the SIMPONI SmPC and Section 2 of the Patient Leaflet) are sufficient to manage the risk.

- Clinical recommendations for the management of colon carcinoma/dysplasia are included in European guidelines (Magro 2017; ECCO 2021).

Rationale for Removal of Missing Information "Long-term safety in adult patients with UC"

- SIMPONI has been approved for the treatment of adult patients with UC and has been used in clinical practice for this indication for more than 10 years.

- Reviews of postmarketing data from the GMS global safety database and the published literature did not identify any new risks that impact the benefit-risk balance of SIMPONI during long-term use in adult patients with UC.

- The MK-8259-013 and MK-8259-042 studies are the only remaining additional pharmacovigilance activities in the SIMPONI EU-RMP to address the missing information "Long-term safety in adult patients with UC". It is not expected that additional pharmacovigilance activities will further inform on the safety profile in this population.

- The long-term safety of SIMPONI in adult patients with UC is therefore no longer considered missing information.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks

- Serious infections
- Demyelinating disorders
- Malignancy

Important potential risks

- Serious depression including suicidality
- Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero

Missing information

- Long-term safety in pediatric patients

The tables in Section SVII.3.1 present the proportion of subjects in clinical trials with events relevant to the important identified and potential risks of SIMPONI.

The column titled 'All Randomized Blinded Trials Population' (referred to as the 'Controlled Portions of Clinical Trials' in Section SIII [Clinical Trial Exposure]) includes the following studies and presents data through the following timepoints:

- Phase 2/3 RA, PsA, AS, and nr-AxSpA SC trials:
  - Through Week 20 for C0524T02
  - Through Week 52 for C0524T05
  - Through Week 24 for C0524T06, C0524T11, C0524T28, C0524T08, C0524T09, and C0524T29

  - Through Week 16 for P07642
- Phase 3 RA IV trials: through Week 24 for C0524T12 and CNTO148ART3001
- Phase 3 PsA IV trial: through Week 24 for CNTO148PSA3001
- Phase 3 AS IV trial: through Week 16 for CNTO148AKS3001
- Phase 2/3 UC trials: Through Week 6 for C0524T16 and C0524T17

Note that there is no 'All Randomized, Blinded Trials Population' column in the tables for the SC asthma trial (C0524T03) since the trial did not have controlled and uncontrolled portions because it was placebo-controlled throughout. Additionally, there is no 'All Randomized, Blinded Trials population' column in the tables for CNTO148JIA3001 since all subjects were exposed to golimumab through Week 16.

The column titled 'All Clinical Trials Population' (referred to as 'Exposure through the End of the Reporting Period' in Section SIII [Clinical Trial Exposure]) includes the following trials and presents the proportion of subjects with relevant events through the end of the trial (unless otherwise specified):

- Phase 2/3 RA, PsA, AS, and nr-AxSpA SC trials:
  - RA: C0524T02, C0524T05, C0524T06, C0524T11, and C0524T28
  - PsA: C0524T08
  - AS: C0524T09 and C0524T29
  - nr-AxSpA: P07642
- Phase 3 RA, PsA, and AS IV trials:
  - RA: C0524T12 and CNTO148ART3001
  - PsA: CNTO148PSA3001
  - AS: CNTO148AKS3001
- Phase 2b asthma SC trial: C0524T03
- Phase 2/3 UC SC and IV trials: C0524T16, C0524T17, and C0524T18
- Phase 3 pJIA SC trial: CNTO148JIA3001

The clinical trial data are presented using Medical Dictionary for Regulatory Activities (MedDRA) Versions 17.0 (for JIA trial) and 19.1 (for adult trials).

Analyses presented in the tables include the incidence, odds ratio, and 95% CI of subjects with relevant events in the clinical trials as well as seriousness, outcome, and severity. The odds ratio was calculated on all randomized, blinded trials populations. However, if the number of events for placebo/active comparator was 0 or the number of events for golimumab was 0 or if the sum of events for placebo/active comparator and the number events for golimumab ≤5, odds ratio was not calculated.

Tables presenting integrated data are included in Section SVII.3.1 for all risks where events were reported in the adult clinical trials in RA, PsA, nr-AxSpA, UC, and asthma. Tables are not presented if there were no events relating to a particular risk in the adult clinical trials; a statement is included in the introductory text to reflect this information.

For the pJIA clinical trial, data for the risks where events were observed are presented in separate tables, except for the risk of demyelinating disorders. For this risk a statement describing the singular event observed in the pJIA trial is included in the introductory text for the risk. Tables are not presented if there were no events relating to a particular risk in the pJIA trial; a statement is included in the introductory text to reflect this information.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Serious Infections

Potential Mechanisms:

Tumor necrosis factor alpha is a mediator of cellular immune responses and inflammation, which are important in host defense against certain pathogens, especially intracellular pathogens. Anti-TNFα agent therapy reduces the ability to mount an inflammatory response against such pathogens. SIMPONI may therefore inhibit protective immune responses to intracellular bacteria (including mycobacteria) and opportunistic pathogens and may also allow HBV reactivation.

Evidence source(s) and Strength of Evidence:

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. Drugs that inhibit TNFα have also been associated with 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.

Characterization of the Risk – Data:

Data for serious infections are presented in the tables below and grouped in the following subcategories: serious infections, opportunistic infections, and TB. No events of HBV reactivation were reported in clinical trials and therefore no tables are presented for this subcategory. In the Phase 3 pJIA trial (CNTO148JIA3001), in addition to no events of HBV reactivation, no events of opportunistic infection or active TB were reported and therefore no tables are provided for these subcategories.

Table SVII.1: Important Identified Risk – Serious Infections – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	3.0% vs 1.9%	10.2% vs 2.1%	0.7% vs 3.5%	3.8% vs 3.5%	0.5% vs 0.5%	4.3% vs 0.5%	0.0% vs 0.0%	1.0% vs 0.0%
Odds ratio (95% CI)	1.531 (0.797, 2.939)	-	0.188 (0.034, 1.041)	-	-	-	-	-
Seriousness/outcomes								
Was Serious	40 (3.0%)	192 (10.2%)	2 (0.7%)	15 (3.8%)	2 (0.5%)	24 (4.3%)	0	2 (1.0%)
Resulted in Death	1 (0.1%)	7 (0.4%)	0	0	0	0	0	0
Did not recover (Persisted)	2 (0.1%)	5 (0.3%)	0	1 (0.3%)	0	1 (0.2%)	0	0
Recovered	37 (2.7%)	180 (9.6%)	2 (0.7%)	14 (3.6%)	2 (0.5%)	23 (4.1%)	0	2 (1.0%)
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	3 (0.2%)	12 (0.6%)	0	0	0	1 (0.2%)	0	0
Moderate	18 (1.3%)	93 (5.0%)	0	8 (2.0%)	2 (0.5%)	13 (2.3%)	0	0
Severe	19 (1.4%)	87 (4.6%)	2 (0.7%)	7 (1.8%)	0	10 (1.8%)	0	2 (1.0%)
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

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Table SVII.2: Important Identified Risk – Serious Infections – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	1.7% vs 0.6%	6.0% vs 0.9%	0.4% vs 0.8%	2.2% vs 0.8%	1.0% vs 0.0%	1.5% vs 0.0%
Odds ratio (95% CI)	2.720 (0.619, 11.956)	-	-	-	-	-
Seriousness/outcomes						
Was Serious	15 (1.7%)	73 (6.0%)	1 (0.4%)	10 (2.2%)	1 (1.0%)	3 (1.5%)
Resulted in Death	0	3 (0.2%)	0	1 (0.2%)	0	0
Did not recover (Persisted)	1 (0.1%)	7 (0.6%)	1 (0.4%)	2 (0.4%)	0	0
Recovered	14 (1.5%)	63 (5.2%)	0	7 (1.5%)	1 (1.0%)	3 (1.5%)
Missing	0	0	0	0	0	0
Severity						
Mild	1 (0.1%)	8 (0.7%)	0	0	0	0
Moderate	7 (0.8%)	33 (2.7%)	0	7 (1.5%)	0	2 (1.0%)
Severe	7 (0.8%)	32 (2.6%)	1 (0.4%)	3 (0.7%)	1 (1.0%)	1 (0.5%)
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

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Table SVII.3: Important Identified Risk – Serious Infections – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	15.6% vs 8.9%	0.8% vs 1.5%	6.8% vs 2.5%	1.5% vs 1.2%	7.1% vs 1.8%
Odds ratio (95% CI)	1.899 (0.809, 4.459)	0.569 (0.196, 1.652)	-	1.245 (0.790, 1.963)	-
Seriousness/outcomes					
Was Serious	36 (15.6%)	8 (0.8%)	85 (6.8%)	68 (1.5%)	456 (7.1%)
Resulted in Death	0	1 (0.1%)	4 (0.3%)	2 (< 0.1%)	17 (0.3%)
Did not recover (Persisted)	2 (0.9%)	0	3 (0.2%)	4 (0.1%)	21 (0.3%)
Recovered	34 (14.7%)	7 (0.7%)	78 (6.3%)	62 (1.4%)	418 (6.6%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	5 (0.4%)	4 (0.1%)	27 (0.4%)
Moderate	9 (3.9%)	4 (0.4%)	44 (3.5%)	30 (0.7%)	218 (3.4%)
Severe	27 (11.7%)	4 (0.4%)	36 (2.9%)	34 (0.7%)	211 (3.3%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

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SVII.4: Important Identified Risk – Serious Infections

	pJIA SC Trial(CNTO148JIA3001)
	Clinical Trial Population n(%) (N=173)
Frequency for golimumab	12 (6.9%)
Seriousness/outcomes	
Was Serious	12 (6.9%)
Resulted in Death	0
Did not recover (Persisted)	0
Recovered	12 (6.9%)
Missing	0
Severity	
Mild	0
Moderate	8 (4.6%)
Severe	4 (2.3%)
Missing	0

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Table SVII.5: Important Identified Risk – Opportunistic Infections – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.1% vs 0.0%	0.7% vs 0.0%	0.0% vs 0.0%	0.8% vs 0.0%	0.0% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	1 (0.1%)	5 (0.3%)	0	3 (0.8%)	0	1 (0.2%)	0	0
Resulted in Death	0	0	0	0	0	0	0	0
Did not recover (Persisted)	1 (0.1%)	4 (0.2%)	0	1 (0.3%)	0	1 (0.2%)	0	0
Recovered	1 (0.1%)	10 (0.5%)	0	2 (0.5%)	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	3 (0.2%)	0	0	0	0	0	0
Moderate	1 (0.1%)	8 (0.4%)	0	1 (0.3%)	0	1 (0.2%)	0	0
Severe	1 (0.1%)	3 (0.2%)	0	2 (0.5%)	0	0	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

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Table SVII.6: Important Identified Risk – Opportunistic Infections – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.1% vs 0.0%	0.6% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	2 (0.2%)	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	2 (0.2%)	0	0	0	0
Recovered	1 (0.1%)	5 (0.4%)	0	0	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	1 (0.1%)	5 (0.4%)	0	0	0	0
Moderate	0	2 (0.2%)	0	0	0	0
Severe	0	0	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

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Table SVII.7: Important Identified Risk – Opportunistic Infections – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.1% vs 0.0%	0.3% vs 0.0%	0.1% vs 0.0%	0.5% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	0	0	2 (0.2%)	1 (< 0.1%)	13 (0.2%)
Resulted in Death	0	0	0	0	0
Did not recover (Persisted)	0	0	0	1 (< 0.1%)	8 (0.1%)
Recovered	0	1 (0.1%)	4 (0.3%)	2 (< 0.1%)	21 (0.3%)
Missing	0	0	0	0	0
Severity					
Mild	0	1 (0.1%)	2 (0.2%)	1 (< 0.1%)	10 (0.2%)
Moderate	0	0	0	1 (< 0.1%)	12 (0.2%)
Severe	0	0	2 (0.2%)	1 (< 0.1%)	7 (0.1%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

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Table SVII.8: Important Identified Risk - Tuberculosis – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.2% vs 0.0%	1.0% vs 0.0%	0.0% vs 0.0%	0.3% vs 0.0%	0.0% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	3 (0.2%)	18 (1.0%)	0	1 (0.3%)	0	2 (0.4%)	0	0
Resulted in Death	0	0	0	0	0	0	0	0
Did not recover (Persisted)	1 (0.1%)	3 (0.2%)	0	0	0	0	0	0
Recovered	2 (0.1%)	16 (0.9%)	0	1 (0.3%)	0	2 (0.4%)	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	2 (0.1%)	0	0	0	0	0	0
Moderate	2 (0.1%)	12 (0.6%)	0	0	0	0	0	0
Severe	1 (0.1%)	5 (0.3%)	0	1 (0.3%)	0	2 (0.4%)	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

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Table SVII.9: Important Identified Risk - Tuberculosis – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.3% vs 0.0%	0.0% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.5% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	4 (0.3%)	0	2 (0.4%)	0	1 (0.5%)
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	2 (0.2%)	0	1 (0.2%)	0	0
Recovered	0	2 (0.2%)	0	1 (0.2%)	0	1 (0.5%)
Missing	0	0	0	0	0	0
Severity						
Mild	0	0	0	0	0	0
Moderate	0	3 (0.2%)	0	2 (0.4%)	0	1 (0.5%)
Severe	0	1 (0.1%)	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

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Table SVII.10: Important Identified Risk - Tuberculosis – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.4% vs 0.0%	0.0% vs 0.0%	0.6% vs 0.0%	0.1% vs 0.0%	0.6% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	1 (0.4%)	0	7 (0.6%)	3 (0.1%)	36 (0.6%)
Resulted in Death	0	0	1 (0.1%)	0	1 (< 0.1%)
Did not recover (Persisted)	0	0	2 (0.2%)	1 (< 0.1%)	8 (0.1%)
Recovered	1 (0.4%)	0	4 (0.3%)	2 (< 0.1%)	28 (0.4%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	2 (0.2%)	0	4 (0.1%)
Moderate	1 (0.4%)	0	4 (0.3%)	2 (< 0.1%)	23 (0.4%)
Severe	0	0	1 (0.1%)	1 (< 0.1%)	10 (0.2%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

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Characterization of the Risk – Discussion:

Serious infections are considered a class effect of anti-TNFα agents. Infections are described in the SIMPONI SmPC (Section 4.3 [Contraindications], Section 4.4 [Special warnings and precautions for use], and Section 4.8 [Undesirable effects]).

In the All Randomized Blinded Trials Population of All Trials with SIMPONI, the frequency of serious infections in golimumab-treated subjects was 1.5% compared with 1.2% for those who received placebo or comparator. Of note, the frequency of opportunistic infections and TB in the All Randomized Blinded Trials Population of All Trials was similar for golimumab-treated subjects and those who received placebo or comparator.

Although patients with a history of latent granulomatous infection, including TB, were generally excluded from clinical trials, patients with a newly positive tuberculin skin test (during screening) or a positive QuantiFERON-TB test were eligible for trial participation in the SC Phase 3 RA, PsA, AS, and nr-AxSpA trials, as well as the IV Phase 3 PsA, AS, and RA trials, if they received appropriate treatment for latent TB prior to or simultaneously with the first administration of trial medication. In the SC Phase 3 trials, 334 subjects had TB prophylaxis, 239 of whom received golimumab; none of these subjects developed active TB. In the IV Phase 3 RA, PsA, and AS trials, a total of 235 subjects had TB prophylaxis and none developed active TB. During the UC trial C0524T18, 7 subjects were diagnosed with active TB; 1 of these subjects was receiving TB prophylactic therapy and died from active TB. None of the other 6 subjects with active TB tested positive for latent TB at screening.

Postmarketing data are consistent with what is currently known about the risk of serious infections in patients treated with SIMPONI. A 5-year trending analysis, covering the period 07 April 2018 to 28 February 2023, of the reporting rate (RR) of spontaneously reported cases of serious infections (including opportunistic infection and TB) in patients exposed to IV and SC SIMPONI in the postmarketing setting showed an overall decrease. For HBV reactivation, similar 5-year postmarketing trending in patients exposed to SC SIMPONI shows a stable profile and no cases involving the IV route were identified during the 5-year reporting period. Based on review of data in the PBRER/PSUR (data lock point: 06 April 2023), no new safety information has been identified for this important identified risk.

The impact of this risk on the individual patient is potentially significant. Patients who are exposed to and subsequently infected with an infectious agent may have a more severe course due to use of the product.

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 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 HIV disease, increased age, having an organ transplant, immunosuppressive drug therapy (corticosteroids, MTX, azathioprine, and biologic agents), chronic pulmonary disease, and chronic renal failure.

Invasive Fungal Infections

People who have resided in or traveled 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, use of corticosteroids or other 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 traveled 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).

Hepatitis B Virus Reactivation

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 (Shibolet 2002). 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 (Ocama 2005).

Preventability:

SIMPONI is contraindicated in patients with active TB or other severe infections such as sepsis and opportunistic infections (SmPC Section 4.3 [Contraindications]). The risk of serious infections is described in the Patient Reminder Card (see Part V.2).

Serious Infections and Opportunistic Infections

Section 4.4 of the SmPC (Special warnings and precautions for use) states that golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and golimumab should not be administered until the infection resolves.

Invasive Fungal Infections

Section 4.4 of the SmPC (Special warnings and precautions for use) states that for patients who have resided in or traveled to regions where invasive fungal infections are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of therapy.

Tuberculosis

Patients who are being considered for golimumab therapy should be evaluated for TB infection. Golimumab should not be given to patients with active TB. Golimumab should not be given to patients with latent TB unless treatment for latent TB is initiated prior to administering golimumab, including those patients with a past history of latent TB in whom an adequate course of treatment cannot be confirmed. Patients receiving golimumab should be monitored closely for signs and symptoms of active TB during and after treatment (SmPC Section 4.4 [Special warnings and precautions for use]).

Hepatitis B Virus Reactivation

All patients should be screened for HBV infection prior to initiation of SIMPONI. In patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of HBV infection is recommended. Chronic carriers of HBV should be appropriately evaluated and monitored prior to initiation of, during treatment with, and for several months following discontinuation of SIMPONI (SmPC Section 4.4 [Special warnings and precautions for use]).

Impact on the Risk-benefit Balance of the Product:

The observed incidence of serious infections has not had a significant impact on the risk-benefit balance of the product. Risk minimization measures are in place and considered adequate and proportionate to the risk; the SmPC and PL provide information to the prescriber and patient on how to manage this important identified risk. In addition, the safety concern is addressed in the Patient Reminder Card.

Public Health Impact:

The public health impact of the development of serious infections during treatment with SIMPONI is not known.

Important Identified Risk: Demyelinating Disorders

Potential Mechanisms:

The role that TNFα plays as an immunomodulator suggests that TNFα blockade may promote the development of drug-induced neuropathies by augmenting the number of activated peripheral T cells and thereby enhancing autoimmune responses by altering antigen presenting cell function, potentiating T-cell receptor signaling, and/or decreasing apoptosis of autoreactive T cells. These autoreactive T cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens (Stübgen 2008).

Evidence Source(s) and Strength of Evidence:

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.

Characterization of the Risk - Data

In the Phase 3 pJIA trial (CNTO148JIA3001), one event of serious demyelination was reported for a subject on Day 770. The outcome of the event was reported as recovering/resolving.

Events that were reported in RA, PsA, AS, nr-AxSpA, asthma, and UC trials are summarized in the tables below.

Table SVII.11: Important Identified Risk - Demyelinating Disorders – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.1% vs 0.0%	0.3% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	0	5 (0.3%)	0	0	0	1 (0.2%)	0	0
Resulted in Death	0	0	0	0	0	0	0	0
Did not recover (Persisted)	1 (0.1%)	5 (0.3%)	0	0	0	2 (0.4%)	0	0
Recovered	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	0	0	0	0	0	0	0
Moderate	0	3 (0.2%)	0	0	0	1 (0.2%)	0	0
Severe	1 (0.1%)	2 (0.1%)	0	0	0	1 (0.2%)	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

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Table SVII.12: Important Identified Risk - Demyelinating Disorders – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.0% vs 0.0%	0.4% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	0	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0
Recovered	0	0	1 (0.4%)	1 (0.2%)	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	0	0	0	0	0	0
Moderate	0	0	1 (0.4%)	1 (0.2%)	0	0
Severe	0	0	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

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Table SVII.13: Important Identified Risk - Demyelinating Disorders – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.0% vs 0.0%	0.2% vs 0.0%	< 0.1% vs 0.0%	0.2% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	0	0	3 (0.2%)	0	9 (0.1%)
Resulted in Death	0	0	0	0	0
Did not recover (Persisted)	0	0	1 (0.1%)	1 (< 0.1%)	8 (0.1%)
Recovered	0	0	2 (0.2%)	1 (< 0.1%)	3 (< 0.1%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	1 (0.1%)	0	1 (< 0.1%)
Moderate	0	0	2 (0.2%)	1 (< 0.1%)	7 (0.1%)
Severe	0	0	0	1 (< 0.1%)	3 (< 0.1%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

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Characterization of the Risk – Discussion:

Demyelinating disorders are considered a class effect for anti-TNFα agents. Demyelinating disorders are listed in the SIMPONI SmPC (Section 4.4 [Special warnings and precautions for use] and Section 4.8 [Undesirable effects]).

In the All Randomized Blinded Trials Population of All Trials with SIMPONI, the frequency of demyelinating disorders was <0.1% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator.

Postmarketing data are consistent with what is currently known about the risk of demyelinating disorders in patients treated with SIMPONI. A 5-year trending analysis, covering the period 07 April 2018 to 28 February 2023, of the RR of spontaneously reported cases of demyelinating disorders in patients exposed to SC SIMPONI showed the RR has been decreasing. Four cases involving the IV route of administration of SIMPONI were identified during the 5-year reporting period. Based on review of data in the PBRER/PSUR (data lock point: 06 April 2023), no new safety information has been identified for the important identified risk of demyelinating disorders.

The impact of this risk on the individual patient can vary from minimal to significant. Patients with pre-existing or recent onset of demyelinating disorders may have a more severe course due to use of the product. This risk needs to be carefully weighed against the benefit conferred by use of the medication.

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 (Didonna 2015). Whites, particularly of northern European descent, are also more likely to develop MS (Ascherio 2016).

Several studies have suggested an association between smoking and MS (Ascherio 2016). Obesity in early life and Epstein-Barr virus have also been identified as risk factors for MS (Ascherio 2016).

Preventability:

Predictability and preventability of the development of demyelination is not known. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNFα agents should be carefully considered before initiation of SIMPONI therapy (SmPC Section 4.4 [Special warnings and precautions for use]).

Impact on the Risk-benefit Balance of the Product:

Demyelinating disorders is an unusual risk that is being evaluated in ongoing additional pharmacovigilance (PV) activities. Risk minimization measures are in place and considered adequate and proportionate to the risk. The SmPC and PL provide information to the prescriber and patient on how to manage this important identified risk.

Public Health Impact:

The public health impact of the development of demyelinating disorders during treatment with SIMPONI is not known.

Important Identified Risk: Malignancy

As part of the broad term of malignancy, information relating to specific subtypes of malignancy (lymphoma, hepatosplenic T-cell lymphoma [HSTCL], skin cancer, and leukemia) are described in this section of the RMP. These subtypes are identified as ADRs in the SIMPONI SmPC and were previously listed as important identified risks (Lymphoma, Skin cancer, and Leukemia) and an important potential risk (Hepatosplenic T-cell lymphoma) in the SIMPONI RMP.

Potential Mechanisms:

Immunomodulation by TNFα may be important in tumor surveillance, although the literature is not consistent on this point (Torre-Amione 1996). While TNFα was shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumor cell lines, some malignant cell lines are TNFα-resistant or even proliferate in the presence of low levels of TNFα and TNFα may behave as a tumor promoter particularly in the setting of unresolved, chronic inflammation (Balkwill 2006). Therefore, 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.

Of note, HSTCL is a rare and rapidly progressive subtype of peripheral T-cell lymphoma and has been reported following TNFα-blocker therapy. Most patients who developed HSTCL were adolescent or young adult males. Almost all these patients had also received azathioprine or 6-mercaptopurine. Hypothetical mechanisms include (1) inhibition of TNF signaling resulting in impaired immune surveillance particularly affecting the detection and elimination of cells with chromosomal abnormalities resulting from azathioprine or 6-mercaptopurine therapy and (2) alterations in azathioprine or 6-mercaptopurine metabolism in patients receiving anti-TNF therapy (Shale 2008).

Evidence Source(s) and Strength of Evidence:

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 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 (Geborek 2005; Bongartz 2006). However, there is an increased background risk for lymphoma in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation (Wolfe 2004; Hemminki 2008a; Hyrich 2018). 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 (Hemminki 2008b).

For 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.

Characterization of the Risk - Data:

Data for malignancies are presented in the tables below and grouped in the following subcategories: malignancies (excluding lymphoma, skin cancer, and leukemia), lymphoma, skin cancer (NMSC and melanoma skin cancer), and leukemia. No events of HSTCL were reported and therefore no tables are presented for this subcategory.

In the Phase 3 pJIA trial (CNTO148JIA3001), no events of malignancy were reported and therefore no tables for this pediatric study are included in this section.

Table SVII.14: Malignancy (Excluding Lymphoma, Skin Cancer, and Leukemia) – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.2% vs 0.6%	1.8% vs 0.6%	0.3% vs 0.0%	2.8% vs 0.0%	0.3% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	0.339 (0.076, 1.521)	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	3 (0.2%)	33 (1.8%)	1 (0.3%)	11 (2.8%)	1 (0.3%)	2 (0.4%)	0	0
Resulted in Death	0	5 (0.3%)	0	2 (0.5%)	0	1 (0.2%)	0	0
Did not recover (Persisted)	2 (0.1%)	18 (1.0%)	0	3 (0.8%)	1 (0.3%)	1 (0.2%)	0	0
Recovered	1 (0.1%)	10 (0.5%)	1 (0.3%)	6 (1.5%)	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	1 (0.1%)	1 (0.3%)	1 (0.3%)	0	0	0	0
Moderate	0	5 (0.3%)	0	3 (0.8%)	0	1 (0.2%)	0	0
Severe	3 (0.2%)	27 (1.4%)	0	7 (1.8%)	1 (0.3%)	1 (0.2%)	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

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Table SVII.15: Malignancy (Excluding Lymphoma, Skin Cancer, and Leukemia) – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.1% vs 0.0%	0.6% vs 0.0%	0.0% vs 0.8%	0.4% vs 0.8%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	1 (0.1%)	7 (0.6%)	0	2 (0.4%)	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	4 (0.3%)	0	0	0	0
Recovered	1 (0.1%)	3 (0.2%)	0	2 (0.4%)	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	0	0	0	0	0	0
Moderate	0	3 (0.2%)	0	1 (0.2%)	0	0
Severe	1 (0.1%)	4 (0.3%)	0	1 (0.2%)	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

Adapted from: [TSFRMPPR02B.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part2.sas] 19JAN2018, 19:10

Table SVII.16: Malignancy (Excluding Lymphoma, Skin Cancer, and Leukemia) – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	1.7% vs 0.0%	0.1% vs 0.0%	0.9% vs 0.2%	0.2% vs 0.3%	1.1% vs 0.3%
Odds ratio (95% CI)	-	-	-	0.553 (0.186, 1.648)	-
Seriousness/outcomes					
Was Serious	3 (1.3%)	1 (0.1%)	11 (0.9%)	7 (0.2%)	71 (1.1%)
Resulted in Death	0	0	3 (0.2%)	0	11 (0.2%)
Did not recover (Persisted)	3 (1.3%)	0	1 (0.1%)	3 (0.1%)	32 (0.5%)
Recovered	1 (0.4%)	1 (0.1%)	7 (0.6%)	4 (0.1%)	29 (0.5%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	1 (0.1%)	1 (< 0.1%)	3 (< 0.1%)
Moderate	1 (0.4%)	1 (0.1%)	2 (0.2%)	1 (< 0.1%)	16 (0.3%)
Severe	3 (1.3%)	0	8 (0.6%)	5 (0.1%)	53 (0.8%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

Adapted from: [TSFRMPPR02C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part3.sas] 19JAN2018, 19:18

Table SVII.17: Lymphoma (Excluding HSTCL) - Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.1% vs 0.0%	0.4% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	2 (0.1%)	8 (0.4%)	0	0	0	1 (0.2%)	0	0
Resulted in Death	0	3 (0.2%)	0	0	0	0	0	0
Did not recover (Persisted)	2 (0.1%)	4 (0.2%)	0	0	0	0	0	0
Recovered	0	1 (0.1%)	0	0	0	1 (0.2%)	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	1 (0.1%)	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Severe	2 (0.1%)	7 (0.4%)	0	0	0	1 (0.2%)	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

Adapted from: [TSFRMPIR08A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part1.sas] 19JAN2018, 18:55

Table SVII.18: Lymphoma (Excluding HSTCL) - Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	0	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0
Recovered	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	0	0	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

Adapted from: [TSFRMPIR08B.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part2.sas] 19JAN2018, 19:10

Table SVII.19: Lymphoma (Excluding HSTCL) - Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.4% vs 0.0%	0.0% vs 0.0%	0.2% vs 0.0%	< 0.1% vs 0.0%	0.2% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	1 (0.4%)	0	2 (0.2%)	2 (< 0.1%)	12 (0.2%)
Resulted in Death	0	0	0	0	3 (< 0.1%)
Did not recover (Persisted)	1 (0.4%)	0	2 (0.2%)	2 (< 0.1%)	7 (0.1%)
Recovered	0	0	0	0	2 (< 0.1%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	1 (0.1%)	0	2 (< 0.1%)
Moderate	0	0	0	0	0
Severe	1 (0.4%)	0	1 (0.1%)	2 (< 0.1%)	10 (0.2%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

Adapted from: [TSFRMPIR08C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part3.sas] 19JAN2018, 19:18

Table SVII.20: Nonmelanoma Skin Cancers – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.4% vs 0.6%	1.5% vs 0.6%	0.7% vs 0.0%	2.5% vs 0.0%	0.3% vs 0.5%	0.4% vs 0.5%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	0.567 (0.152, 2.118)	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	4 (0.3%)	24 (1.3%)	2 (0.7%)	10 (2.5%)	1 (0.3%)	2 (0.4%)	0	0
Resulted in Death	0	0	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	2 (0.5%)	0	0	0	0
Recovered	5 (0.4%)	28 (1.5%)	2 (0.7%)	8 (2.0%)	1 (0.3%)	2 (0.4%)	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	4 (0.3%)	14 (0.7%)	2 (0.7%)	7 (1.8%)	1 (0.3%)	1 (0.2%)	0	0
Moderate	1 (0.1%)	12 (0.6%)	0	3 (0.8%)	0	1 (0.2%)	0	0
Severe	0	2 (0.1%)	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

Adapted from: [TSFRMPIR10A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part1.sas] 19JAN2018, 18:55

Table SVII.21: Nonmelanoma Skin Cancers – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.3%	0.2% vs 0.3%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	1 (0.1%)	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0
Recovered	0	3 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	0	3 (0.2%)	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

Adapted from: [TSFRMPIR10B.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part2.sas] 19JAN2018, 19:10

Table SVII.22: Nonmelanoma Skin Cancers – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.9% vs 0.0%	0.1% vs 0.0%	0.4% vs 0.0%	0.2% vs 0.3%	0.8% vs 0.3%
Odds ratio (95% CI)	-	-	-	0.632 (0.219, 1.825)	-
Seriousness/outcomes					
Was Serious	1 (0.4%)	0	1 (0.1%)	7 (0.2%)	40 (0.6%)
Resulted in Death	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	2 (< 0.1%)
Recovered	2 (0.9%)	1 (0.1%)	5 (0.4%)	8 (0.2%)	49 (0.8%)
Missing	0	0	0	0	0
Severity					
Mild	2 (0.9%)	1 (0.1%)	4 (0.3%)	7 (0.2%)	32 (0.5%)
Moderate	0	0	1 (0.1%)	1 (< 0.1%)	17 (0.3%)
Severe	0	0	0	0	2 (< 0.1%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

Adapted from: [TSFRMPIR10C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part3.sas] 19JAN2018, 19:18

Table SVII.23: Melanoma – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.0% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	0	2 (0.1%)	0	0	0	0	0	0
Resulted in Death	0	0	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0	0	0
Recovered	0	3 (0.2%)	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	2 (0.1%)	0	0	0	0	0	0
Moderate	0	1 (0.1%)	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

Adapted from: [TSFRMPIR09A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part1.sas] 19JAN2018, 18:55

Table SVII.24: Melanoma – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	0	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0
Recovered	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	0	0	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

Adapted from: [TSFRMPIR09B.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part2.sas] 19JAN2018, 19:10

Table SVII.25: Melanoma – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.4% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.1% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	1 (0.4%)	0	0	0	3 (< 0.1%)
Resulted in Death	0	0	0	0	0
Did not recover (Persisted)	1 (0.4%)	0	0	0	1 (< 0.1%)
Recovered	0	0	0	0	3 (< 0.1%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	0	0	2 (< 0.1%)
Moderate	0	0	0	0	1 (< 0.1%)
Severe	1 (0.4%)	0	0	0	1 (< 0.1%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

Adapted from: [TSFRMPIR09C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part3.sas] 19JAN2018, 19:18

Table SVII.26: Leukemia – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	0	1 (0.1%)	0	0	0	0	0	0
Resulted in Death	0	1 (0.1%)	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0	0	0
Recovered	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	0	0	0	0	0	0	0
Moderate	0	1 (0.1%)	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

Adapted from: [TSFRMPIR16A.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part1.sas] 19JAN2018, 18:55

Table SVII.27: Leukemia – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.1% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	0	1 (0.1%)	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0
Recovered	0	1 (0.1%)	0	0	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	0	0	0	0	0	0
Moderate	0	1 (0.1%)	0	0	0	0
Severe	0	0	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

Adapted from: [TSFRMPIR16B.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part2.sas] 19JAN2018, 19:10

Table SVII.28: Leukemia – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	< 0.1% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	0	0	0	0	2 (< 0.1%)
Resulted in Death	0	0	0	0	1 (< 0.1%)
Did not recover (Persisted)	0	0	0	0	0
Recovered	0	0	0	0	1 (< 0.1%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	0	0	0
Moderate	0	0	0	0	2 (< 0.1%)
Severe	0	0	0	0	0
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

Adapted from: [TSFRMPIR16C.rtf] [CNTO148\Z_RMP\DBR_AKSPSA_FINAL\RE_AKSPSA_FINAL\rmp_risks_part3.sas] 19JAN2018, 19:18

Characterization of the Risk – Discussion:

The risk of malignancy is addressed in the SIMPONI SmPC (Section 4.4 [Special warnings and precautions for use] and/or Section 4.8 [Undesirable effects]) and certain subtypes of malignancies are listed as ADRs.

In the All Randomized, Blinded Trials Population of All Trials with SIMPONI, the frequencies of certain types of malignancies were as follows:

- Malignancies (excluding lymphoma, skin cancer, and leukemia): 0.2% for golimumab-treated subjects compared with 0.3% for those who received placebo or comparator.
- Lymphoma (excluding HSTCL): <0.1% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator.
- Skin cancer:
  - Nonmelanoma skin cancer: <0.2% for golimumab-treated subjects compared with 0.3% for those who received placebo or comparator.
  - Melanoma skin cancer: 0.0% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator.
- Leukemia: 0.0% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator.

In the postmarketing setting, 5-year trending analyses (07 April 2018 to 28 February 2023) of spontaneously reported cases have shown the following:

- Malignancies (excluding lymphoma, HSTCL, skin cancer, and leukemia): overall downward trend of the RR in patients exposed to SC SIMPONI and overall downward trend of the RR in patients exposed to IV SIMPONI.
- Lymphoma (excluding HSTCL): overall downward trend of the RR in patients exposed to SC SIMPONI. The low number of cases received for IV administration (6) was insufficient to identify a trend.
- Skin cancer: overall downward trend of the RR in patients exposed to IV and SC SIMPONI.
- Leukemia: overall downward trend in RR of spontaneously reported cases in patients exposed to SC SIMPONI. Two cases were reported in patients exposed to IV SIMPONI during the same reporting period.

No cases of HSTCL have been identified in clinical trials or the postmarketing setting for SIMPONI through 28 February 2023.

In summary, postmarketing data for malignancies are consistent with what is currently known about the risk of malignancies in patients treated with SIMPONI. Based on review of data in the PBRER/PSUR (data lock point: 06 April 2023), no new safety information has been identified for this important identified risk.

The impact of this risk on the individual patient is potentially significant, particularly in patients with an existing malignancy, a history of malignancy, or significant risk factors for malignancy such as a history of heavy smoking.

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 (Jones 1996; Tennis 1993; Silman 1988). 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 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 DMARD (Moder 1995).

Information regarding additional risk factors for the malignancy subtypes included in the broad category of malignancy is given below.

Lymphoma

- 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, Sjögren's 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*, *Chlamydophila psittaci*, *Campylobacter jejuni*, chronic hepatitis C infection), radiation exposure, and exposure to certain chemicals among others (Baecklund 2006; Smedby 2006; Hartge 2007; Cerhan 2014; American Cancer Society, 2018).
- Hepatosplenic T-cell lymphoma: young men, the immunocompromised, and patients undergoing solid organ transplantation appear to be at a higher risk for HSTCL (Belhadj 2003).

Skin Cancer

- 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 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 (American Cancer Society, 2016).

- 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 (Wrone 2011). 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 (Wolfe 2007). With respect to psoriasis patients, a higher risk of NMSC is seen in those with prior coal tar, UVB therapy, psoralen plus UVA light, retinoids, and cyclosporine therapy (Stern 1998; Nijsten 2003; Curtin 2005).
- 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 (Duprat 2011; Wang 2011). 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 (Wang 2011).

Leukemia

- 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 (Choi 2014; Elbæk 2016).

Preventability:

Predictability and preventability of the development of malignancy is not known. Caution should be exercised when considering the use of SIMPONI in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy (SmPC Section 4.4 [Special warnings and precautions for use]).

For skin cancer, specific preventive measures can be taken such as limiting sun exposure, especially in the middle of the day (between the hours of 10 am and 4 pm). Also, use of sunscreen, protective clothing, and hats are recommended to limit exposure to UV light. Periodic skin examinations are recommended for all patients, particularly for patients with risk factors for skin cancer.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of malignancy (including lymphoma, HSTCL, skin cancer and leukemia) has not had a significant impact on the risk-benefit balance of the product. It is expected that the risk of malignancy will be further characterized by the PV activities outlined in this RMP. Leukemia is well characterized and based upon the small number of events reported to date, there is limited possibility of further characterization. Risk minimization measures are in place and considered adequate and proportionate to the risk; the SmPC and PL provide information to the prescriber and patient on how to manage the important identified risk of malignancy.

Public Health Impact:

The public health impact of the development of malignancy during treatment with SIMPONI is not known.

Important Potential Risk: Serious Depression Including Suicidality

Potential Mechanisms:

The exact biological mechanism of depression is not known. Cytokines may be involved with serotonin metabolism (Dantzer 1999). More specifically, pro-inflammatory cytokines such as TNFα are associated with major depression; reducing the effect of these cytokines may reverse depressive symptoms (Tyring 2006). The mechanism by which SIMPONI could affect mood is not known.

Evidence Source(s) and Strength of Evidence:

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 (Isik 2007; Sundquist 2008; Kotsis 2012). 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 IBD (Sajadinejad 2012; Román 2011).

Characterization of the Risk – Data:

Events that were reported in RA, PsA, AS, nr-AxSpA, asthma, UC, and pJIA trials are summarized in the tables below.

Table SVII.29: Important Potential Risk - Serious Depression (Including Suicidality) – Part 1; Treated Subjects Across Indications

	RA SC Trials		PsA SC Trial		AS SC Trials		nrAxSpA SC Trial	
	All Randomized, Blinded Trials Population n (%) (N=1355)	All Clinical Trials Population n (%) (N=1877)	All Randomized, Blinded Trials Population n (%) (N=292)	All Clinical Trials Population n (%) (N=394)	All Randomized, Blinded Trials Population n (%) (N=386)	All Clinical Trials Population n (%) (N=564)	All Randomized, Blinded Trials Population n (%) (N=97)	All Clinical Trials Population n (%) (N=193)
Frequency[a]								
Golimumab vs Placebo/Comparator[b]	0.1% vs 0.0%	0.3% vs 0.0%	0.0% vs 0.0%	0.5% vs 0.0%	0.8% vs 0.0%	0.9% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-	-	-
Seriousness/outcomes								
Was Serious	2 (0.1%)	6 (0.3%)	0	2 (0.5%)	3 (0.8%)	5 (0.9%)	0	0
Resulted in Death	0	0	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	1 (0.3%)	1 (0.2%)	0	0
Recovered	2 (0.1%)	6 (0.3%)	0	2 (0.5%)	2 (0.5%)	4 (0.7%)	0	0
Missing	0	0	0	0	0	0	0	0
Severity								
Mild	0	1 (0.1%)	0	0	0	1 (0.2%)	0	0
Moderate	0	1 (0.1%)	0	0	1 (0.3%)	1 (0.2%)	0	0
Severe	2 (0.1%)	4 (0.2%)	0	2 (0.5%)	2 (0.5%)	3 (0.5%)	0	0
Missing	0	0	0	0	0	0	0	0

[a] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b] The denominators for the combined comparator groups are: RA SC - Randomized, Blinded (N=616), RA SC - All Clinical Trials (N=616), PsA SC - Randomized, Blinded (N=113), PsA SC - All Clinical Trials (N=113), AS SC - Randomized, Blinded (N=182), AS SC - All Clinical Trials (N=182), nrAxSpA SC - Randomized, Blinded (N=100), nrAxSpA SC - All Clinical Trials (N=100).

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Table SVII.30: Important Potential Risk - Serious Depression (Including Suicidality) – Part 2; Treated Subjects Across Indications

	RA IV Trials[a]		PsA IV Trials		AS IV Trials	
	All Randomized, Blinded Trials Population n (%) (N=908)	All Clinical Trials Population n (%) (N=1213)	All Randomized, Blinded Trials Population n (%) (N=240)	All Clinical Trials Population n (%) (N=460)	All Randomized, Blinded Trials Population n (%) (N=105)	All Clinical Trials Population n (%) (N=204)
Frequency[b]						
Golimumab vs Placebo/Comparator[c]	0.1% vs 0.0%	0.2% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%	0.0% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-	-
Seriousness/outcomes						
Was Serious	1 (0.1%)	3 (0.2%)	0	0	0	0
Resulted in Death	0	0	0	0	0	0
Did not recover (Persisted)	0	0	0	0	0	0
Recovered	1 (0.1%)	3 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0
Severity						
Mild	1 (0.1%)	1 (0.1%)	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	2 (0.2%)	0	0	0	0
Missing	0	0	0	0	0	0

[a] Data for C0524T12 is through Week 48 database lock which includes only the IV portion of the trial.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: RA IV - Randomized, Blinded (N=326), RA IV - All Clinical Trials (N=326), PsA IV - Randomized, Blinded (N=239), PsA IV - All Clinical Trials (N=239), AS IV - Randomized, Blinded (N=103), AS IV - All Clinical Trials (N=103).

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Table SVII.31: Important Potential Risk - Serious Depression (Including Suicidality) – Part 3; Treated Subjects Across Indications

	Asthma SC Trial[a]	UC SC and IV Trials		All Trials	
	All Clinical Trials Population n (%) (N=231)	All Randomized, Blinded Trials Population n (%) (N=947)	All Clinical Trials Population n (%) (N=1245)	All Randomized, Blinded Trials Population n (%) (N=4560)	All Clinical Trials Population n (%) (N=6381)
Frequency[b]					
Golimumab vs Placebo/Comparator[c]	0.0% vs 0.0%	0.0% vs 0.0%	0.4% vs 0.0%	0.1% vs 0.0%	0.3% vs 0.0%
Odds ratio (95% CI)	-	-	-	-	-
Seriousness/outcomes					
Was Serious	0	0	5 (0.4%)	6 (0.1%)	21 (0.3%)
Resulted in Death	0	0	0	0	0
Did not recover (Persisted)	0	0	0	1 (< 0.1%)	1 (< 0.1%)
Recovered	0	0	5 (0.4%)	5 (0.1%)	20 (0.3%)
Missing	0	0	0	0	0
Severity					
Mild	0	0	1 (0.1%)	1 (< 0.1%)	4 (0.1%)
Moderate	0	0	1 (0.1%)	1 (< 0.1%)	3 (< 0.1%)
Severe	0	0	3 (0.2%)	4 (0.1%)	14 (0.2%)
Missing	0	0	0	0	0

[a] The asthma SC trial (C0524T03) is placebo-controlled throughout.
[b] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[c] The denominators for the combined comparator groups are: SC - Asthma - All Clinical Trials (N=79), UC Trials - Randomized, Blinded (N=407), UC Trials - All Clinical Trials (N=407), All Trials - Randomized, Blinded (N=2165), All Trials - All Clinical Trials (N=2165).

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Table SVII.32: Important Potential Risk - Serious Depression (Including Suicidality)

	pJIA SC Trial (CNTO148JIA3001)
	Clinical Trial Population n (%) (N=173)
Frequency for golimumab	1 (0.6%)
Seriousness/outcomes	
Was Serious	1 (0.6%)
Resulted in Death	0
Did not recover (Persisted)	0
Recovered	1 (0.6%)
Missing	0
Severity	
Mild	0
Moderate	1 (0.6%)
Severe	0
Missing	0

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Characterization of the Risk – Discussion:

In the All Randomized, Blinded Trials Population of All Trials with SIMPONI, the frequency of serious depression (including suicidality) was <0.1% for golimumab-treated subjects compared with 0.0% for those who received placebo or comparator.

Postmarketing data are consistent with what is currently known about the risk of serious depression (including suicidality) in patients treated with SIMPONI. A 5-year trending analysis, covering the period 07 April 2018 to 28 February 2023, of the RR of spontaneously reported cases of serious depression (including suicidality) in patients exposed to SC SIMPONI showed a downward trend. Three cases of serious depression (including suicidality) involving the IV route of administration of SIMPONI was identified during the 5-year reporting period. Based on review of data in the PBRER/PSUR (data lock point: 06 April 2023), no new safety information has been identified for the important identified risk of serious depression (including suicidality). Depression is listed in the SIMPONI SmPC (Section 4.8 [Undesirable effects]).

The impact of this risk on the individual patient can vary from minimal to considerable. This risk needs to be carefully weighed against the benefit conferred by use of the medication.

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 (Fancher 2007).

Preventability:

There is no known means of preventing depression. There are screening tools available to identify patients with depression. Patients with a history of untreated or inadequately treated depression should be treated for such.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of serious depression, including suicidality has not had a significant impact on the risk-benefit balance of the product. The safety concern is being evaluated in an ongoing additional PV activity, and routine risk minimization measures that are considered adequate and proportionate to the risk are in place.

Public Health Impact:

The public health impact of the development of serious depression (including suicidality) during treatment with SIMPONI is not known.

Important Potential Risk: Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero

Potential Mechanisms:

Following treatment with a TNFα-blocking mAb during pregnancy, the antibody was detected for up to 6 months in the serum of the infant born to the treated woman. Because TNFα inhibitors reduce the immune response, administration of a TNFα inhibitor during pregnancy may predispose infants to breakthrough infections when receiving live (attenuated) vaccines within 6 months after birth. It is known that SIMPONI crosses the placenta during pregnancy and so this risk may also apply to SIMPONI.

Evidence Source and Strength of Evidence:

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 (REMICADE SmPC Section 4.4). A cumulative search of the postmarketing safety database from launch through 28 February 2023 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.

Characterization of the Risk – Data and Discussion:

There have been no reported cases of breakthrough infections following administration of live (attenuated) vaccines in infants born to women who received SIMPONI in clinical trials or in the postmarketing setting from launch through 28 February 2023.

Women who were pregnant, nursing, or planning a pregnancy were excluded from SIMPONI clinical trials. In addition, if a woman became pregnant while participating in a clinical trial, the study agent was discontinued.

Breakthrough infection after administration of live (attenuated) vaccines in infants exposed to TNFα inhibitors in utero, including SIMPONI, is considered a class effect. It is considered an important potential risk because the impact of this risk is potentially significant.

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.

Preventability:

Administration of live (attenuated) vaccines to infants exposed to SIMPONI in utero is not recommended for 6 months following the mother's last SIMPONI injection during pregnancy (SmPC Section 4.6 [Fertility, pregnancy and lactation]). The risk of breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero is described in the Patient Reminder Card (see Part V.2).

Impact on the Risk-benefit Balance of the Product:

As there are no reported cases through 28 February 2023, breakthrough infection after administration of live (attenuated) vaccines in infants with in utero exposure to SIMPONI has not had a significant impact on the risk-benefit balance of the product. Risk minimization measures are in place and considered adequate and proportionate to the risk; the SmPC, PL, and Patient Reminder Card provide information to the prescriber and patient on how to manage this important potential risk.

Public Health Impact:

The potential public health impact is not known.

SVII.3.2. Presentation of the Missing Information

Missing information: Long-term safety in pediatric patients
Evidence source: Comorbidities of patients with pJIA differ from those of non-pJIA patients and therefore the long-term safety profile of golimumab in patients with pJIA may differ from that in other indications. A relatively small number of children ≥2 to <18 years of age (173) were exposed to golimumab in the pJIA trial CNTO148JIA3001, in which the average duration of follow-up for randomized subjects was 107 weeks. Although no risks of clinical significance were identified in golimumab-treated subjects, the effect of long-term treatment with golimumab in this patient population has not been studied.
Population in need of further characterization: Pediatric patients ≥2 years of age who have been treated with SIMPONI long term. An observational postauthorization safety study (PASS) to investigate the long-term safety of golimumab in pJIA subjects using the German Biologics JIA Registry (BiKeR), in which patients are followed for up to 5 years, is ongoing.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Serious infections
	Demyelinating disorders
	Malignancy
Important Potential Risks	Serious depression including suicidality
	Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero
Missing Information	Long-term safety in pediatric patients

PART III: PHARMACOVIGILANCE PLAN
(Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	Purpose/Description
Serious infections	TOI TFUQ to collect information on serious infections and opportunistic infections TOI TFUQ to collect information on TB TOI TFUQ to collect information on progressive multifocal leukoencephalopathy/reversible posterior leukoencephalopathy syndrome
Malignancy	TOI TFUQ to collect information on malignancy events (including lymphoma, second and secondary malignancies). Particular attention is paid to subjects ≤30 years of age.

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
Not applicable.		

III.2. Additional Pharmacovigilance Activities

Study name and title	MK-8259-050: An observational post-approval safety study of golimumab in treatment of pJIA using the German Biologics JIA Registry (BiKeR)
Rationale and study objectives	To investigate the long-term safety of golimumab in pJIA subjects by comparing the risks of primary safety endpoints (serious infections, malignancy, autoimmune processes, and exposure during pregnancy) in the golimumab cohort with those in the comparator cohorts (contemporary anti-TNF cohort, contemporary MTX cohort, and historic anti-TNF cohort), adjusted for baseline characteristics. Secondary objectives include the crude incidence of: • Demyelinating disorders • Serious depression including suicidality
Safety concerns addressed	• Serious infections • Malignancy • Long-term safety in pediatric patients
Study design	Observational cohort study using the German Biologics JIA Registry (Biologika in der Kinderrheumatologie [BiKeR])

Study population	Patients with pJIA who newly initiate therapy with SIMPONI, other anti-TNFα agents, or MTX, and are enrolled in the German BiKeR registry. In addition, the study will include a historic cohort of patients (extracted from the BiKeR database) treated with anti-TNFα agents.
Milestones	Next progress report: December 2022 and periodically thereafter. Study finish: December 2026 Final report: June 2027

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
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) Ongoing	To investigate the long-term safety of golimumab in pJIA subjects by comparing the risks of primary safety endpoints (serious infections, malignancy, autoimmune processes, and exposure during pregnancy) in the golimumab cohort with those in the comparator cohorts (contemporary anti-TNF cohort, contemporary MTX cohort, and historic anti-TNF cohort), adjusted for baseline characteristics. Secondary objectives will include crude incidence rates of: • Demyelinating disorders • Serious depression including suicidality	• Serious infections • Malignancies • Long-term safety in pediatric patients	Final report	June 2027

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorizations				
Not applicable.				
Efficacy studies which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				

PART V: RISK MINIMIZATION MEASURES
(Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious infections	**Routine risk communication:** SmPC sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) Package Leaflet (PL) sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special warnings and precautions for use) • Guidance on evaluating patients for infections prior to treatment initiation, monitoring patients for infections during and after treatment, and managing patients who develop infections SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction) • Recommendations regarding the administration of live vaccines to patients receiving SIMPONI PL sections 2 and 4 • Patients are advised to notify their doctor if they have an infection before using SIMPONI or if they experience symptoms of an infection during SIMPONI treatment. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Demyelinating disorders	**Routine risk communication:** SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special warnings and precautions for use) • Guidance to discontinue use of SIMPONI if demyelinating disorders develop PL sections 2 and 4 • Patients are advised to notify their doctor if they have been diagnosed with nervous system disease before using SIMPONI or if they experience any symptoms of nervous system disease. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription
Malignancy	**Routine risk communication:** SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) PL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.4 (Special warnings and precautions for use) • Recommendation to screen patients with UC who are at increased risk for or have a history of colon dysplasia or colon carcinoma for dysplasia before treatment initiation and throughout their disease course • Recommendation to perform periodic skin examination PL section 2 • Patients are advised to notify their doctor have been diagnosed with lymphoma or any other cancer before using SIMPONI or if they experience symptoms of lymphoma, skin cancer, or leukemia. Patients who may be at increased risk for cancer should discuss with their doctor whether treatment with a TNF blocker is appropriate. PL section 4 • Patients are advised to notify their doctor if they experience symptoms of lymphoma, skin cancer, or leukemia. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Serious depression including suicidality	**Routine risk communication:** SmPC section 4.8 (Undesirable effects) PL section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription
Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero	**Routine risk communication:** SmPC sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy, and lactation) PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC section 4.6 (Fertility, pregnancy, and lactation) • Recommendations regarding the administration of live vaccines to infants exposed to golimumab in utero PL section 2 • Patients who take SIMPONI while pregnant are advised tell their baby's doctor and other HCPs about their use of SIMPONI before their baby receives any vaccine. **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription
Long-term safety in pediatric patients	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Restricted medical prescription

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity: Patient Reminder Card	
Objectives:	The goal of the Patient Reminder Card is to educate patients on important safety information that they need to be aware of before and during treatment with SIMPONI. The Patient Reminder Card addresses the following important risks: • Serious infections (including opportunistic infections, tuberculosis, hepatitis B virus reactivation) • Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero
Rationale for the additional risk minimization activity:	To enhance patient knowledge regarding the risk of infection associated with SIMPONI treatment and to remind patients who received SIMPONI during pregnancy to inform their infant's physician before the infant receives any live vaccine.
Target audience and planned distribution path:	The Patient Reminder Card is provided as part of the product packaging.
Plans to evaluate the effectiveness of the interventions and criteria for success:	None

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infections	**Routine risk minimization measures:** • SmPC sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) • Package Leaflet (PL) sections 2 and 4 **Additional risk minimization measures:** Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ for Serious Infections and Opportunistic Infections TOI TFUQ for TB TOI TFUQ for Progressive Multifocal Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS) **Additional pharmacovigilance activities:** MK-8259-050

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Demyelinating disorders	**Routine risk minimization measures:** • SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) • PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MK-8259-050
Malignancy	**Routine risk minimization measures:** • SmPC sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) • PL sections 2 and 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ for Malignancies (including Lymphoma, Second and Secondary Malignancies) **Additional pharmacovigilance activities:** MK-8259-050
Serious depression including suicidality	**Routine risk minimization measures:** • SmPC section 4.8 (Undesirable effects) • PL section 4 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MK-8259-050
Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero	**Routine risk minimization measures:** • SmPC sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy, and lactation) • PL section 2 **Additional risk minimization measures:** Patient Reminder Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term safety in pediatric patients	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** MK-8259-050

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 be:

- 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 - the amount of medicine in a single pack which is chosen to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including in Periodic Benefit Risk Evaluation Reports/Periodic Safety Update Reports assessments 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 Breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero
Missing information	Long-term safety in pediatric patients

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 traveled 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 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 traveled 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>

Important Identified Risk: Serious infections	
	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 sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and 4.8 (Undesirable effects) Package Leaflet sections 2 and 4 Additional risk minimization measures: Patient Reminder Card
Additional pharmacovigilance activities	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 sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) Package Leaflet sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	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 reports of lymphoma, skin cancer, and leukemia, have been received during 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 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

Important Identified Risk: Malignancy	
	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 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

Important Identified Risk: Malignancy	
	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, Sjögren 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 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.

Important Identified Risk: Malignancy	
	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 sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) Package Leaflet sections 2 and 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	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) Package Leaflet section 4 Additional risk minimization measures: None
Additional pharmacovigilance activities	MK-8259-050 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 28 February 2023 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 sections 4.4 (Special warnings and precautions for use) and 4.6 (Fertility, pregnancy, and lactation) Package Leaflet section 2 Additional risk minimization measures: Patient Reminder Card
Additional pharmacovigilance activities	None

Missing information: Long-term safety in pediatric patients	
Risk minimization measures	Routine risk minimization measures: Not applicable. Additional risk minimization measures: Not applicable.
Additional pharmacovigilance activities	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
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)	To investigate the long-term safety of golimumab in pJIA subjects by comparing the risks of primary safety endpoints (serious infections, malignancy, autoimmune processes, and exposure during pregnancy) in the golimumab cohort with those in the comparator cohorts (contemporary anti-TNF cohort, contemporary MTX cohort, and historic anti-TNF cohort), adjusted for baseline characteristics. To address the safety concerns of: • Serious infections • Malignancies • Long-term safety in pediatric patients Secondary objectives will include crude incidence rates of: • Demyelinating disorders • Serious depression including suicidality

PART VII: ANNEXES

Annex 4: Specific Adverse Reaction Follow-up Questionnaires

Table of Contents

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Serious Infections and Opportunistic Infections

Manufacturer Control Number: Drug generic (TRADENAME):
Date of Report: [dd-MMM-yyyy]

1. Medical History and Concurrent Conditions

☐ Prior history of exposure to TB
Details:
☐ Prior history of exposure to Hepatitis B/C
Details:
Details of vaccination history:
☐ The patient was considered immunocompromised *(underlying diagnoses, immunosuppressive therapy etc.)*
Details:

Other relevant medical history or any known risk factors for acquiring specific infection in question:

2. Adverse Event Details

☐ The infection was present prior to starting the product

☐ There were unusual features of the patient's presentation or clinical course
Details:

Type of infection (e.g., pneumonia, endocarditis, etc.) and location if relevant (e.g., subcutaneous abscess of the forearm or TB of the CNS):

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Tuberculosis (TB)

Manufacturer Control Number: Drug generic (TRADE) Name:
Date of Report [dd-MMM-yyyy]

1. **Relevant medical/occupational history** *(Check all that apply and provide details below.)*

- ☐ Weight loss ≥ 10% of ideal body weight
- ☐ Diabetes
- ☐ Gastrectomy or jejunoileal bypass
- ☐ Organ/Tissue transplant
- ☐ Prior BCG vaccination
- ☐ Recent travel to endemic area
- ☐ Head/Neck carcinoma
- ☐ Leukemia/Lymphoma
- ☐ Household contact/Exposure to TB
- ☐ Prior/prolonged steroid use
- ☐ IV drug abuse
- ☐ Prior/prolonged immunosuppressant use`
- ☐ Silicosis
- ☐ Positive HIV test
- ☐ Resident/employee at high risk setting (e.g., correctional institute, homeless shelter, nursing home, refugee camp, etc.)

Details:

2. **Diagnostics**

☐ Purified Protein Derivative (PPD) testing was performed. Indicate test used:

- ☐ Intradermal skin test
- ☐ Multipuncture skin test

Number of units administered:

PPD Result: mm of induration (0, if no induration)

Date of PPD: [dd-MMM-yyyy]

2nd PPD results (if applicable): mm of induration

Date of second PPD: [dd-MMM-yyyy]

☐ False negative test (e.g., time of injection to time of evaluation too long/short, evaluator of induration, etc.)? Explain reasons:

☐ The subject had active TB

☐ Prophylactic therapy was given

Time elapsed from onset of TB symptoms to institution of treatment:

Type of tuberculosis:

- ☐ Pulmonary
- ☐ Extrapulmonary; Location:
- ☐ Disseminated; Location:
- ☐ Multi-drug Resistant TB

Other laboratory results

Laboratory Test		Test Result	Date: [dd-MMM-yyyy]
AFB Smear	Sputum		
	Other (specify)		
Culture	Sputum		
	Other (specify)		
PCR MTb			
Quantiferon TB Gold			

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Progressive Multifocal Leukoencephalopathy (PML)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Manufacturer Control Number: Drug generic (TRADE) Name:
Date of Report: [dd-MMM-yyyy]

1. Medical History and Concurrent Conditions

List relevant concurrent/pre-existing conditions *(e.g., Hodgkin's CLL, CML, AML, ongoing GVHD, long term immunosuppression, pre-existing neurological features/disorders, and any relevant previous imaging or laboratory test results.) List the details with dates of diagnosis*:

History of pre-existing conditions (*Check all that apply*):

- ☐ Systemic hypertension
- ☐ Renal disease (e.g., renal failure)
- ☐ Preceding history of infection (e.g., HIV and/or sepsis)
- ☐ Immune mediated disease (e.g., Systemic lupus erythematosus, Polyarteritis nodosa etc.)

Other relevant medical history (e.g., transplantation, neurological disorders, pre-eclampsia, chemotherapy etc.):

2. Diagnostics

Laboratory/radiographic evaluation results as appropriate and accompanying normal ranges, if available. *(Note date performed and other test results as appropriate.)*

- ☐ MRI: Date: [dd-MMM-yyyy], Results:
- ☐ JC Virus DNA test was performed: Date: [dd-MMM-yyyy], Results:
- ☐ CSF Fluid: Date: [dd-MMM-yyyy], Results:
- ☐ Brain tissue biopsy: Date: [dd-MMM-yyyy], Results:
- ☐ Non-CSF sources for JCV DNA testing: Date: [dd-MMM-yyyy], Results:
- ☐ Imaging studies (e.g., CT scan, etc.): Date: [dd-MMM-yyyy], Results:
- ☐ Histopathology of brain biopsy finding: Date: [dd-MMM-yyyy]
  - ☐ Demyelination
  - ☐ Enlarged oligodendroglial nuclei
  - ☐ Bizarre astrocytes
  - ☐ Other findings:
- ☐ Evidence of JC virus in brain tissue by:
  - ☐ Electron microscopy
  - ☐ Immunohistochemistry
  - ☐ In situ Hybridization
  - ☐ PCR
- ☐ Other relevant test results:
- ☐ Neurological evaluation was performed. (*Include the neurology report*):
- ☐ Other findings, including dates *(e.g., clinical features observed - central nervous system and other symptoms and their progression, including dates [these could include neurological deficits such as motor symptoms (e.g., hemiparesis), cognitive dysfunction or changes in behavior or personality, language or speech disturbances (e.g., aphasia/dysarthria), visual disturbances (e.g., hemianopsia), ataxia/loss of motor coordination, seizures, etc.])*:

MCN:

3. **Prior or Concurrent Immunosuppressant Medications** *(e.g., chemotherapy agents, radiation, transplant regimens, immunotherapy with monoclonal antibodies such as anti-CD-20 monoclonal antibodies and include over-the-counter and herbal medications).*

Medication	Indication	Total Daily Dose	Start Date [dd-MMM-yyyy]	Stop Date [dd-MMM-yyyy]

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Malignancies (including Lymphoma, Second and Secondary Malignancies)

Manufacturer Control Number: Drug generic (TRADENAME):

Date of Report: [dd-MMM-yyyy]

1. **Relevant Medical/Family History** *(Provide prior diagnoses and details for checked items below)*

- ☐ Previous malignancy (Provide specific diagnosis):
- ☐ Occupational/Exposure history:
- ☐ Excessive sun exposure (Describe):
- ☐ History of PUVA (Psoralen + Ultraviolet-A rays)
- ☐ History of radiation
  - Dose of radiation:
  - Area treated:
  - Age (or date of therapy) of the patient when they were treated with radiation:
  - Indication for radiation:
  - Any radiation induced changes?
- ☐ Pre-malignant lesions, e.g., Barret's oesophagus, Bowen's disease. Details:

Viral infections: ☐ EBV ☐ HIV ☐ HPV ☐ HBV or HCV

- ☐ Other relevant risk factors for malignancy (Excluding medications):
- ☐ Family history of malignancy (Provide specific diagnoses for each):
  - ☐ In first degree relatives:
  - ☐ In more distant relatives:
- ☐ Previous history of tumor necrosis factor (TNF) blocker therapy (With medication names, dates of exposure and the total number of doses or an approximation):

Age at first exposure to any TNF blocker:

☐ Previous administration of other immunosuppressive medications, antineoplastic medications, or other drugs, which have a risk for malignancy stated in their label. (e.g., other biologics, methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, prednisone, or other)

Include drug indication, dose levels, and treatment duration (e.g., methotrexate, clophosphamide, vincristine, doxorubicine, cyclosporine, biologics)

Medication	Indication	Dose/Route of Administration	Start Date/Stop Date (dd-MMM-yyyy)

- ☐ Cytogenetic abnormalities detected at any point in time? (Include those relevant for any malignancy including myeloma – this could be germline genetic diseases predisposing for malignancy e.g., Down's syndrome, neurofibromatosis etc., or cytogenetic abnormalities relevant to myeloma)

2. Diagnostics

Histopathologic diagnosis (Include the histopathology report):

Include malignancy stage, location of primary tumor, metastases, lymph node involvement and staging system used:

Additional diagnostic information, including finding that support specified staging; specialty consultations (Attach reports, if available): Final diagnosis:

☐ **Lymphoma**

☐ Non-Hodgkin's lymphoma

Histologic subtype: Immunophenotype: Cytogenetics:

☐ Hodgkin's lymphoma

Histologic subtype:

Was the lymphoma tissue tested for Epstein-Barr virus (EBV) (e.g., by in situ hybridization and/or immunohistology analysis)? ☐ No ☐ Yes (Attach report)

If Yes, Test Result: ☐ EBV positive ☐ EBV negative

☐ **Second malignancy** (A cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy) (List):

☐ **Secondary malignancy** (A cancer caused by treatment for a previous malignancy e.g., Treatment with radiation or chemotherapy. It is NOT considered a metastasis of the initial malignancy) (*List*):

(Ref.http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf)

Malignancy screening/Preventive measures (Include those that are relevant to the specific malignancy that is being reported, e.g., recent mammography, breast exam, Pap smear, sigmoidoscopy or colonoscopy, faecal occult blood, Prostatic Specific Antigen, digital rectal exam, HPV vaccine etc.)

Screening Test/Preventive Measure	Date (dd-MMM-yyyy)	Results (Including units and reference ranges where applicable)

3. Treatment

What was the response to the first treatment for malignancy?

☐ Complete response ☐ Partial response ☐ Stable disease ☐ Progressive disease

Annex 6: Details of Additional Risk Minimization Activities

Approved Key Messages of the Additional Risk Minimization Measures

Patient Reminder Card

The educational program consists of a Patient Reminder Card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professionals (HCPs) treating the patient, about ongoing treatment with the product.

The Patient Reminder Card shall contain the following key messages:

- A reminder to patients to show the Patient Reminder Card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using SIMPONI.
- Provision to record the type, date and result of TB screenings.
- A statement that the brand name and batch number should be recorded.
- That treatment with SIMPONI may increase the risks of serious infections, opportunistic infections, TB, HBV reactivation, and breakthrough infection after administration of live vaccines in infants exposed to golimumab in utero and when to seek attention from an HCP.
- Contact details of the prescriber.

The language of the Patient Reminder Card is included in the SIMPONI product information Annex IIIA.