PRODUCT MONOGRAPH

SIMPONI®
golimumab injection

Solution for Subcutaneous Injection

50 mg/0.5 mL
100 mg/1.0 mL

SIMPONI® I.V.
golimumab for injection

Solution for Intravenous Infusion
50 mg/4.0 mL

Tumour necrosis factor alpha (TNFα) inhibitor

SIMPONI® should be prescribed by physicians who have sufficient knowledge of rheumatoid arthritis and/or ankylosing spondylitis and/or psoriatic arthritis and/or non-radiographic axial spondyloarthritis and/or ulcerative colitis and who have fully familiarized themselves with the efficacy/safety profile of SIMPONI ®.

SIMPONI® I.V. should be prescribed by physicians who have sufficient knowledge of rheumatoid arthritis and/or ankylosing spondylitis and/or psoriatic arthritis and who have fully familiarized themselves with the efficacy/safety profile of SIMPONI ® I.V.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
Subcutaneous injection (SC)	50 mg / 0.5 mL SmartJect® Autoinjector	sorbitol, L-histidine, L-histidine hydrochloride, polysorbate 80, water for injection *For a complete listing, see* **Dosage Forms, Composition and Packaging** *section.*
	50 mg / 0.5 mL pre-filled syringe	
	100 mg / 1.0 mL SmartJect® Autoinjector	
	100 mg / 1.0 mL pre-filled syringe	
Intravenous infusion (IV)	50 mg / 4.0 mL vial	sorbitol, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injection *For a complete listing, see* ***Dosage Forms, Composition and Packaging*** *section.*

Golimumab administered through intravenous infusion will be referred to throughout the Product Monograph as SIMPONI® I.V. Golimumab administered subcutaneously will be referred to throughout the Product Monograph as SIMPONI®.

DESCRIPTION

Golimumab is a human IgG1κ monoclonal antibody that exhibits multiple glycoforms with predicted molecular masses ranging from 149,802 daltons to 151,064 daltons. Golimumab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses. Golimumab forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF, which prevents the binding of TNF to its receptors. Golimumab does not bind or neutralize human lymphotoxin. Golimumab inhibits TNF-induced activation of human endothelial cells and human diploid fibroblasts, and significantly reduces clinical symptoms and joint degradation in a human TNF transgenic mouse model of arthritis.

Autoinjector / Pre-filled syringe
SIMPONI® is supplied as a single-use sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. The syringe is fitted with a passive safety guard or contained in a single-use autoinjector. SIMPONI® does not contain preservatives.

Vial
SIMPONI® I.V. is supplied as a sterile solution in single-use vials. SIMPONI® I.V. does not contain preservatives.

INDICATIONS AND CLINICAL USE

SIMPONI®

Rheumatoid Arthritis (RA):

SIMPONI®, in combination with methotrexate (MTX), is indicated for:
- Reducing signs and symptoms and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
- Inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who had not previously been treated with MTX.

Psoriatic Arthritis (PsA):

SIMPONI® is indicated for:
- Reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active psoriatic arthritis. SIMPONI® can be used in combination with MTX in patients who do not respond adequately to MTX alone.

Ankylosing Spondylitis (AS):

SIMPONI® is indicated for:
- Reducing signs and symptoms in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapies.

Non-radiographic Axial Spondyloarthritis (nr-Ax SpA):

SIMPONI® is indicated for:
The treatment of adults with severe active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative Colitis (UC):

SIMPONI® is indicated in adult patients with moderately to severely active disease who have had an inadequate response to, or have medical contraindications for, conventional therapy including corticosteroids, amino salicylates, azathioprine (AZA), or 6-mercaptopurine (6-MP), for:

- Inducing and maintaining clinical response (reduction in signs and symptoms);
- inducing clinical remission;
- Achieving sustained clinical remission in induction responders;
- Improving endoscopic appearance of the mucosa during induction (see **CLINICAL TRIALS**).

SIMPONI® I.V.

Rheumatoid Arthritis (RA):

SIMPONI® I.V., in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

Psoriatic Arthritis (PsA):

SIMPONI® I.V., alone or in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active psoriatic arthritis.

Ankylosing Spondylitis (AS):

SIMPONI® I.V. is indicated for the treatment of adult patients with ankylosing spondylitis who have had an inadequate response or intolerance to conventional therapies.

Geriatrics (≥65 years of age):

See **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics.**

Pediatrics (<18 years of age):

The safety and efficacy of SIMPONI®/ SIMPONI® I.V. have not been established in pediatric patients aged 17 years and younger.

CONTRAINDICATIONS

- Patients with severe infections such as sepsis, tuberculosis and opportunistic infections (see **WARNINGS AND PRECAUTIONS, Infections**).
- Patients with moderate or severe (NYHA class III/IV) congestive heart failure (see **WARNINGS AND PRECAUTIONS, Cardiovascular).**
- Patients who are hypersensitive to golimumab, or any other ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION, AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Infections

- **Serious infections leading to hospitalization or death, including sepsis, tuberculosis (TB), invasive fungal, and other opportunistic infections have been observed with the use of TNF antagonists including golimumab. Administration of SIMPONI®/SIMPONI® I.V. should be discontinued if a patient develops a serious infection or sepsis. Treatment with SIMPONI®/SIMPONI® I.V. should not be initiated in patients with active infections including chronic or localized infections (see Infections section below).**
- **Physicians should exercise caution when considering the use of SIMPONI®/ SIMPONI® I.V. in patients with a history of recurring or latent infections, including TB, or with underlying conditions, which may predispose patients to infections, who have resided in regions where TB and invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic.**
- **Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including golimumab. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection.**
- **Before starting treatment with SIMPONI®/SIMPONI® I.V., all patients should be evaluated for both active and latent tuberculosis.**
- **If latent tuberculosis is diagnosed, treatment for latent tuberculosis should be started with anti-tuberculosis therapy before initiation of SIMPONI®/ SIMPONI® I.V.**
- **Physicians should monitor patients receiving SIMPONI®/SIMPONI® I.V. for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection.**

Malignancy

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which golimumab is a member.**

Infections

Bacterial (including sepsis and pneumonia), mycobacterial (tuberculosis), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving TNF-blocking agents, including golimumab. Patients have frequently presented with disseminated rather than localized disease. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections.

SIMPONI®/SIMPONI® I.V. should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of SIMPONI®/SIMPONI® I.V. 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 must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with SIMPONI®/SIMPONI® I.V. must not be given if a patient develops a serious infection or sepsis.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent tuberculosis infections prior to treatment with SIMPONI®/SIMPONI® I.V. Treatment of latent tuberculosis infections should be initiated prior to therapy with SIMPONI®/SIMPONI® I.V.

Anti-tuberculosis therapy should be considered prior to initiation of SIMPONI®/SIMPONI® I.V. in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Tests for latent tuberculosis may yield false negative results, especially in patients who are immunocompromised or severely ill. Prior to initiating SIMPONI®/SIMPONI® I.V., treatment for latent TB should be considered in patients who have significant risk factors for TB despite a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

In patients receiving SIMPONI®/SIMPONI® I.V., tuberculosis has frequently presented as disseminated or extrapulmonary disease. Cases of active tuberculosis have occurred in patients treated with SIMPONI®/SIMPONI® I.V. during and after treatment for latent tuberculosis. Patients receiving SIMPONI®/SIMPONI® I.V. should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

Opportunistic Infections
Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of SIMPONI®/SIMPONI® I.V. treatment should be carefully considered before initiation or continuation of SIMPONI®/SIMPONI® I.V. therapy.

In at-risk patients treated with SIMPONI®/SIMPONI® I.V., an invasive fungal infection should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localized disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made, if feasible, in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Hepatitis B Virus (HBV) Reactivation
As observed with the use of other immunosuppressive drugs, the use of TNF-blocking agents, including golimumab has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of the virus (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants. Patients should be tested for HBV infection before initiating treatment with immunosuppressants, including SIMPONI®/SIMPONI® I.V. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of, during treatment with, and for several months following discontinuation of SIMPONI®/SIMPONI® I.V.

<u>Malignancies</u>

The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

Pediatric Malignancy
Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which golimumab is a member. Approximately half of the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression,

and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine, or 6 mercaptopurine. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports.

Lymphoma
In the controlled portions of clinical trials of all the TNF-blocking agents including SIMPONI®, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the SIMPONI® Phase 2 and Phase 3 clinical trials in RA, PsA and AS, the incidence of lymphoma in SIMPONI®-treated patients was higher than expected in the general population. Patients with rheumatoid arthritis and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of these cases have occurred in patients with Crohn's disease or ulcerative colitis. The majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF-blocker at or prior to diagnosis. The potential risk with the combination of AZA or 6-MP and SIMPONI® should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Leukemia
Cases of acute and chronic leukemia have been reported with TNF-blocker use, including SIMPONI®/SIMPONI® I.V., in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately two-fold) than the general population for the development of leukemia.

Non-lymphoma Malignancy
In the controlled portions of the SIMPONI® Phase 2 and Phase 3 clinical trials in RA, PsA, AS, and UC, and SIMPONI® I.V. Phase 3 clinical trials in RA, PsA and AS, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the SIMPONI® and the control groups.

In an exploratory clinical trial evaluating the use of SIMPONI® in patients with severe persistent asthma, more patients treated with SIMPONI® reported malignancies compared with control patients. The significance of this finding is unknown.

Colon Dysplasia/Carcinoma
It is not known if SIMPONI® treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon

carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with SIMPONI®/SIMPONI® I.V. the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

Skin Cancers
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocking agents, including golimumab. (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Cardiovascular

Congestive Heart Failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. Cases of CHF in patients with known cardiovascular risk factors have been observed with SIMPONI®/SIMPONI® I.V. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF blocker-treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI®/SIMPONI® I.V. has not been studied in patients with CHF. SIMPONI®/SIMPONI® I.V. should be used with caution in patients with heart failure. If a decision is made to administer SIMPONI®/SIMPONI® I.V. to patients with heart failure, they should be closely monitored during therapy, and SIMPONI®/SIMPONI® I.V. should be discontinued if new or worsening symptoms of heart failure appear.

Concurrent Administration with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, etanercept, with an increased risk of neutropenia and no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. Therefore, the combination of SIMPONI®/SIMPONI® I.V. and anakinra is not recommended (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Concurrent Administration with Abatacept

In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Because of the nature of the adverse events seen with the combination of TNF-blocking agents and abatacept therapy, the combination of SIMPONI®/SIMPONI® I.V. and abatacept is not recommended (See **DRUG INTERACTIONS, Drug-Drug Interactions).**

Concurrent Administration with other Biological Therapeutics

There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as SIMPONI®/SIMPONI® I.V. The concomitant use of SIMPONI®/SIMPONI® I.V. with these biologics is not recommended because of the possibility of an increased risk of infection.

Switching between Biological Therapeutics

When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

Hematologic Reactions

There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anemia and thrombocytopenia in patients receiving TNF-blockers, including golimumab. In clinical studies, cases of pancytopenia, leukopenia, neutropenia and thrombocytopenia have occurred in SIMPONI® I.V. treated patients. Caution should be exercised in patients treated with SIMPONI®/SIMPONI® I.V. who have a current or past history of significant cytopenias. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of SIMPONI®/SIMPONI® I.V. therapy should be considered in patients with confirmed significant hematologic abnormalities.

Immune

Immunosuppression
The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In Phase 1 RA studies, in 81 patients evaluated, there were no substantial differences between subjects receiving SIMPONI® and placebo with respect to responses to delayed-type hypersensitivity antigens. The impact of treatment with golimumab on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Immunizations
Live Vaccines/Therapeutic Infectious Agents
Patients treated with SIMPONI® /SIMPONI® I.V. may receive concurrent vaccinations, except for live vaccines.

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections. It is recommended that live vaccines not be given concurrently with SIMPONI®/SIMPONI® I.V.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with SIMPONI®/SIMPONI® I.V.

Non-live Vaccines

Psoriatic arthritis patients treated with SIMPONI® in one Phase 3 PsA study were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine. Similar numbers of psoriatic arthritis patients receiving SIMPONI® and not receiving SIMPONI® had at least a two-fold increase in antibody titers. The proportions of patients with response to pneumococcal vaccine were lower among SIMPONI® and control-treated patients receiving MTX compared with patients not receiving MTX. Overall, the data indicate that SIMPONI® does not suppress the humoral immune response to this vaccine.

Allergic Reactions

Hypersensitivity Reactions

Allergic reactions (e.g., rash, urticaria, and rarely anaphylaxis and serum sickness-like reactions) have been observed in patients treated with TNF-blocking agents. In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following SIMPONI® administration. Some of these reactions occurred after the first administration of SIMPONI®. If any serious allergic or anaphylactic reaction occurs, administration of SIMPONI®/SIMPONI® I.V. should be discontinued immediately and appropriate therapy initiated.

Latex Sensitivity

The needle cover on the pre-filled syringe as well as the pre-filled syringe in the autoinjector contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Autoimmune Processes

Treatment with TNF blockers, including golimumab may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms of a lupus-like syndrome following treatment with SIMPONI®/SIMPONI® I.V., treatment should be discontinued (see **ADVERSE REACTIONS, Immune,** Autoantibodies).

Autoimmune hepatitis has been reported for other members of the anti-TNFα class.

Demyelinating Disorders

Use of TNF-blocking agents, of which golimumab is a member, have been associated with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS), optic neuritis and peripheral demyelinating disorders, including Guillain-Barré syndrome. In clinical trials, cases of central demyelination, MS, and peripheral demyelinating polyneuropathy have been reported in patients treated with SIMPONI® and SIMPONI® I.V. Prescribers should exercise caution in considering the use of TNF blockers, including SIMPONI®/SIMPONI® I.V. in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI®/SIMPONI® I.V. should be considered if these disorders develop.

Sexual Function/Reproduction

It is not known whether golimumab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study conducted in mice using the analogous anti-mouse TNFα antibody.

Surgery

There is limited safety experience of SIMPONI®/SIMPONI® I.V. treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on SIMPONI®/SIMPONI® I.V. should be closely monitored for infections, and appropriate actions should be taken.

Special Populations

Pregnant Women

An embryo-fetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the first trimester at dosages up to 50 mg/kg twice weekly (over 500-fold higher in terms of dose/body weight ratio than the proposed clinical dose of 50 mg every 4 weeks). The mean peak maternal serum concentration obtained in this study (1,576 µg/mL) is over 900-fold higher than median steady-state C_{max} value (1.71 µg/mL) following 50 mg every 4-week subcutaneous (SC) dosing in patients with RA, PsA, and AS. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. Fetal serum concentrations were approximately 50% of the maternal serum concentrations. In this study, in utero exposure to golimumab produced no developmental defects to the fetus.

A pre- and postnatal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. The mean peak maternal serum concentration obtained in this study (1,482 µg/mL) is over 860-fold higher than median steady-state C_{max} value (1.71 µg/mL) following 50 mg every 4-week SC dosing in patients with RA, PsA, and AS. Golimumab was detected in the breast milk at concentrations that were approximately 350-fold lower than the maternal serum concentrations. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants.

Golimumab crosses the placenta. Following treatment with another TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated women. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see **WARNINGS AND PRECAUTIONS**).

There have been no studies in pregnant women. It is not known whether SIMPONI®/SIMPONI®

I.V. can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI®/SIMPONI® I.V. should be given to a pregnant woman only if clearly needed.

Nursing Women
In a pre- and post-natal developmental toxicology study in cynomolgus monkeys golimumab was detected in the breast milk at concentrations that were approximately 350-fold lower than the maternal serum concentrations.

It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMPONI®/SIMPONI® I.V., women must not breast feed during and for at least 6 months after golimumab treatment. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age)
The safety and efficacy of SIMPONI®/SIMPONI® I.V. have not been established in pediatric patients aged 17 years and younger.

Geriatrics (≥65 years of age)
In the Phase 3 SIMPONI® trials in RA, PsA, and AS and in the Phase 3 SIMPONI® I.V. trial in RA, no overall differences in AEs, SAEs, and serious infections in patients age 65 or older who received SIMPONI®/SIMPONI® I.V. were observed compared with younger patients. In the Phase 3 SIMPONI® I.V. trials in PsA and AS, there were insufficient numbers of patients aged 65 years and over to determine whether they respond differently from patients aged 18 to 65 years old. In UC, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. There were no patients aged 65 and over in the nr-Ax SpA trial.

Women of Childbearing Potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Renally and Hepatically Impaired
Specific studies of SIMPONI®/SIMPONI® I.V. have not been conducted in these patient populations. SIMPONI® /SIMPONI® I.V. should be used with caution in subject with impaired hepatic function.

<u>Monitoring and Laboratory Tests</u>

There is no known interference between SIMPONI®/SIMPONI® I.V. and laboratory tests.

Effects on Ability to Drive and Use Machines

No studies on the effect on the ability to drive and use machines have been performed. SIMPONI®/SIMPONI® I.V. may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of SIMPONI®/SIMPONI® I.V.

Potential for Medication Errors

SIMPONI® is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in **DOSING AND ADMINISTRATION**. Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data from golimumab trials that include Phase 3 SIMPONI® I.V. and Phase 2 and 3 SIMPONI® clinical trials are available from 6161 SIMPONI® I.V. or SIMPONI®-treated patients including 3090 with rheumatoid arthritis, 634 with psoriatic arthritis, 768 with ankylosing spondylitis, 193 with active non-radiographic axial spondyloarthritis (nr-Ax SpA), 1240 with ulcerative colitis and 231 with severe persistent asthma.

The three SIMPONI® I.V. RA, PsA and AS trials included 539 control-treated patients and 740 SIMPONI® I.V.-treated patients.

Through week 54 of the UC trials, 16% of patients who received SIMPONI® reported one or more serious adverse events (SAEs). The most common SAEs were ulcerative colitis (7.6%), anaemia (0.6%) and appendicitis (0.3%) The proportion of subjects with SAEs was higher in the SIMPONI® 100 mg maintenance group compared with golimumab 50 mg maintenance group and placebo groups (16% vs. 8% and 8%, respectively).

Through the controlled period of the SIMPONI® I.V. trials in RA, PsA and AS (through Week 16 in AS and through Week 24 in RA and PsA), the proportion of subjects with 1 or more SAEs was 3.8% in the combined SIMPONI® I.V. group and 2.4% in the placebo group. The most common SAE in SIMPONI® I.V.-treated patients was pneumonia (0.3%).

Upper respiratory tract infection was the most common adverse reaction reported in the controlled period of the Phase 3 IV RA, PsA and AS trials, occurring in 5% of SIMPONI® I.V.-treated patients as compared with 4% of control-treated patients. Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 SC RA, PsA and AS trials through Week 16, occurring in 7% and 6% of SIMPONI®-treated patients as compared with 6% and 5% of control-treated patients, respectively. Nasopharyngitis was the most common adverse reaction reported in the controlled Phase 2/3 UC trials through week 6 occurring in 2.5% of SIMPONI®-treated patients as compared with 2.9% of control-treated patients.

In the Phase 3 trial in nr-Ax SpA, no new ADRs were identified and the frequency/incidence of ADRs was comparable to that observed in patients with RA, PsA, AS and UC.

In general, the overall safety profile was similar for patients receiving SIMPONI® I.V. and SIMPONI®.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

RA, AS and PsA

Table 1 summarizes the adverse drug reactions that occurred at a rate equal to or higher than 1% in SIMPONI® groups and at a frequency higher than the placebo group during the placebo-controlled period of the Phase 3 SIMPONI® studies in RA, AS and PsA, respectively.

TABLE 1: Adverse Drug Reactions Reported by ≥ 1% of Patients in the Phase 3 Trials of RA, PsA, and AS through Week 16[a]

	Placebo ± DMARDs	SIMPONI® ± DMARDs
Patients treated	639	1659
Adverse Reaction		
Blood and lymphatic system disorders		
Anemia	6 (0.9%)	20 (1.2%)
Central and peripheral nervous system		
Dizziness	7 (1.1%)	32 (1.9%)
Paraesthesia	3 (0.5%)	27 (1.6%)
Gastrointestinal system disorders		
Constipation	2 (0.3%)	18 (1.1%)
General disorders and administration site conditions		
Injection site reaction (injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation, paresthesia)	14 (2.2%)	97 (5.8%)
Non-serious allergic reactions	7 (1.1%)	24 (1.4%)
Pyrexia	4 (0.6%)	20 (1.2%)
Infections and Infestations		
Bacterial infections (such as cellulitis)	6 (0.9%)	24 (1.4%)
Bronchitis	9 (1.4%)	31 (1.9%)

TABLE 1: Adverse Drug Reactions Reported by ≥ 1% of Patients in the Phase 3 Trials of RA, PsA, and AS through Week 16[a]

	Placebo ± DMARDs	SIMPONI® ± DMARDs
Sinusitis	8 (1.3%)	27 (1.6%)
Superficial fungal infections	8 (1.3%)	31 (1.9%)
Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinitis)	84 (13.1%)	258 (15.6%)
Viral infections (such as influenza and herpes)	20 (3.1%)	75 (4.5%)
Investigations		
Alanine aminotransferase increased	18 (2.8%)	58 (3.5%)
Aspartate aminotransferase increased	10 (1.6%)	44 (2.7%)
Skin and subcutaneous tissue disorders		
Alopecia	4 (0.6%)	18 (1.1%)
Rash	16 (2.5%)	49 (3.0%)
Vascular disorders		
Hypertension	10 (1.6%)	51 (3.1%)

[a] Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low-dose corticosteroids (≤10 mg of prednisone/day or equivalent, and/or NSAIDs during the trials).

Table 2 summarizes the adverse drug reactions that occurred at a rate equal to or higher than 1% in the SIMPONI® I.V. ± MTX group with a higher incidence than in the placebo ± MTX group during the placebo-controlled period of the Phase 3 SIMPONI® I.V. trials in RA, PsA and AS with a 2 mg/kg dosing regimen.

TABLE 2: Adverse Drug Reactions Reported by ≥1% of SIMPONI® I.V.-Treated Patients and with a Higher Incidence than Placebo-Treated Patients in the Phase 3 Trials of RA (GO-FURTHER) and PsA (GO-VIBRANT) through Week 24 and AS (GO-ALIVE) through Week 16

	Placebo ± MTX	SIMPONI® I.V. ± MTX
Patients Treated	539	740
Adverse Reaction		
Blood and Lymphatic Disorders		
Neutrophil count decrease	5 (0.9%)	13 (1.8%)
Infections and Infestations		
Upper respiratory tract infection (such as upper respiratory tract infection, nasopharyngitis, pharyngitis, laryngitis, and rhinitis)	46 (8.5%)	96 (13.0%)
Viral infections (such as influenza and herpes)	20 (3.7%)	37 (5.0%)
Bronchitis	6 (1.1%)	13 (1.8%)
Sinusitis	5 (0.9%)	13 (1.8%)
Investigations		

TABLE 2:	Adverse Drug Reactions Reported by ≥1% of SIMPONI® I.V.-Treated Patients and with a Higher Incidence than Placebo-Treated Patients in the Phase 3 Trials of RA (GO-FURTHER) and PsA (GO-VIBRANT) through Week 24 and AS (GO-ALIVE) through Week 16	
	Placebo ± MTX	**SIMPONI® I.V. ± MTX**
Alanine aminotransferase increased	12 (2.2%)	33 (4.5%)
Aspartate aminotransferase increased	8 (1.5%)	20 (2.7%)
Vascular disorders		
Hypertension	11 (2.0%)	26 (3.5%)
Skin and subcutaneous disorders		
Rash	2 (0.4%)	14 (1.9%)
General disorders and administration site conditions		
Pyrexia	3 (0.6%)	10 (1.4%)

In another Phase 3 trial in RA with golimumab administered intravenously, using a different dosing regimen (2 mg/kg and 4 mg/kg q12w), the most common cause of death among SIMPONI® I.V.-treated patients was cardiovascular events (3 out of 8 deaths; 2 subjects in the 4 mg/kg group and 1 subject in the 2 mg/kg group). Otherwise, the overall safety profile was similar to SIMPONI® I.V. 2 mg/kg administered at week 0, 4 and every 8 weeks thereafter.

Ulcerative Colitis (UC)

Table 3 summarizes the adverse drug reactions that occurred at a rate equal to or higher than 1% in SIMPONI® groups and at a frequency higher than the placebo group during the placebo-controlled period of the Phase 3 studies in UC.

TABLE 3: Adverse drug reactions reported by ≥ 1% of patients from ulcerative colitis clinical trials

Adverse Drug Reactions reported by ≥ 1% of Patients in the PURSUIT- Induction Study through Week 6		
Patients Treated	**Placebo (n=330)**	**Golimumab 200/100 mg (n=331)**
Adverse Drug Reaction		
Blood and lymphatic system disorders		
Anemia	7 (2.1%)	9 (2.7%)
General disorders and administration site conditions		
Injection site reaction	3 (0.9%)	10 (3.0%)
Infections and Infestations		
Upper respiratory tract infection	17 (5.2%)	19 (5.7%)

Adverse Drug Reactions reported by ≥ 1% of Patients in the PURSUIT-Maintenance Study through Week 54			
Patients Treated	**Placebo (n=285)**	**Golimumab 100 mg (n=946)**	**Golimumab 50 mg (n=154)**
Adverse Drug Reaction			
Blood and lymphatic system disorders			
Anemia	3 (1.1%)	43 (4.5%)	4 (2.6%)
Leukopenia	5 (1.8%)	25 (2.6%)	3 (1.9%)
Autoantibody positive	6 (2.1%)	31 (3.3%)	6 (3.9%)
Gastrointestinal system disorders			
Constipation	3 (1.1%)	15 (1.6%)	2 (1.3%)
General disorders and administration site conditions			
Pyrexia	8 (2.8%)	35 (3.7%)	6 (3.9%)
Infections and infestations			
Abscess	4 (1.4%)	15 (1.6%)	2 (1.3%)
Bronchitis	5 (1.8%)	17 (1.8%)	6 (3.9%)
Sinusitis	7 (2.5%)	28 (3.0%)	6 (3.9%)
Superficial fungal infections	4 (1.4%)	11 (1.2%)	7 (4.5%)
Upper respiratory tract infection	36 (12.6%)	208 (22.0%)	36 (23.4%)
Viral infections	18 (6.3%)	57 (6.0%)	13 (8.4%)
Investigations			
Alanine aminotransferase increased	4 (1.4%)	15 (1.6%)	3 (2.0%)
Aspartate aminotransferase increased	3 (1.1%)	8 (0.8%)	5 (3.2%)
Skin and subcutaneous tissue disorders			
Rash	9 (3.2%)	36 (3.8%)	10 (6.5%)

Other Clinical Trial Adverse Drug Reactions:
Adverse drug reactions that do not appear in the above tables and that occurred ≥1% in golimumab-treated patients beyond the placebo control period included the following events listed below:

Blood and lymphatic system disorders: leukopenia (including neutropenia)
Infections and Infestations: lower respiratory tract infection (pneumonia)

Deaths

During the placebo-controlled Phase 2 and Phase 3 SIMPONI® trials in RA, PsA, AS and severe,

persistent asthma, there was 1 (0.13%) death among 753 patients in the placebo group and 5 deaths (0.25%) among 2,024 patients in the combined SIMPONI® group. The most common cause of death among SIMPONI®-treated patients (2/5, 40%) was sepsis. In the controlled and uncontrolled Phase 2 and 3 RA, PsA and AS studies through approximately 3 years, there were 21 deaths among 2,363 patients treated with at least one dose of SIMPONI® over an exposure period of 5,714 patient years (0.37 per 100 patient years), and one death among placebo patients over an exposure period of 344 patient years (0.29 per 100 patient years). The most common known cause of death among SIMPONI®-treated patients through approximately 3 years (3 out of 21 patients, 14%) was lung cancer.

Among 1233 UC patients treated with at least one dose of SIMPONI® over an exposure period of 1080 patient years, 4 deaths occurred through Week 54 (0.37 per 100 patient year). Causes of death were: sepsis (2 subjects), tuberculosis (1 subject), and congestive heart failure (1 subject). No deaths occurred among placebo patients (n=407).

Among 599 UC patients treated with at least one dose of SIMPONI® during the study extension (Weeks 54 – 228), 7 deaths were reported (0.44 per 100 patient years). The most common cause of death was cancer (colorectal (2 subjects) and gall bladder). Among 96 UC patients treated with placebo one patient died (0.95 per 100 patient years).

During the controlled period of Phase 3 SIMPONI® I.V. studies in RA, PsA and AS, 3 deaths were reported in placebo-treated subjects and no deaths were reported in SIMPONI® I.V.-treated subjects. In the controlled and uncontrolled portions of these studies, there were 3 deaths among 539 patients in the placebo group (with a median follow-up of 0.40 years) and 5 deaths among the 1028 patients in the combined SIMPONI® I.V. groups (with a median follow-up of 1.2 years).

Injection Site Reactions
In the controlled period of the pivotal trials, 5.1% (123/2392) of golimumab-treated patients had injection site reactions compared with 2.0% (19/969) in control-treated patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

In the controlled and uncontrolled Phase 3 RA, PsA and AS trials through approximately 3 years, 12.4% of SIMPONI®-treated patients (8.6% in the 50 mg dose group) had injection site reactions. In the controlled pivotal trials in RA, PsA, AS, severe persistent asthma, and Phase 2/3 trials in UC, no patients treated with golimumab developed anaphylactic reactions deemed to be related to golimumab.

Administration Reactions
In the controlled periods of the pivotal I.V. trials in RA, PsA and AS, 0.2% of placebo-treated subjects and 2.8% of golimumab-treated subjects had an infusion reaction. The most common infusion reactions were rash and headache. No serious infusion reactions were reported.

Malignancies (See **WARNINGS AND PRECAUTIONS, Malignancies**)
Lymphoma

The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these clinical 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. These results may be confounded by the small number of events, designs of the Phase 3 studies, and different durations of follow-up across treatment groups. The majority of lymphomas occurred in RA Study 2, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease. Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. In the controlled and uncontrolled portions of the Phase 3 IV studies in RA, PsA and AS with a median follow-up of 1.2 years, there were no cases of lymphoma with SIMPONI® I.V.

Malignancies other than lymphoma

In the controlled periods of pivotal trials, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control group. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population. The most frequently observed malignancies in SIMPONI®-treated patients during the Phase 3 trials in RA, PsA, and AS were basal cell carcinoma (19/2226, 0.9%), breast cancer (11/2226, 0.5%) and lung cancer (7/2226, 0.3%).

In the controlled and uncontrolled period of the RA trial through 1.8 years, the incidence of malignancies, other than lymphoma, in SIMPONI® I.V.-treated patients was similar to that expected in the general population and the most frequently observed malignancy in SIMPONI® I.V.-treated patients was basal cell carcinoma. There were no cases of malignancies in SIMPONI® I.V.-treated patients in the PsA and AS trials.

In an exploratory clinical trial involving patients with severe persistent asthma, more patients treated with SIMPONI® had malignancies compared with control patients. The significance of this finding in the asthma population is unknown.

The potential role of TNF-blocking therapy in the development of malignancies is unknown.

Demyelinating Disorders (See **WARNINGS AND PRECAUTIONS, Demyelinating Disorders**)

In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. These results may be confounded by the small number of events, designs of the pivotal trials, and different durations of follow-up across treatment groups.

During the controlled period of Phase 3 RA, PsA and AS SIMPONI® I.V. trials, one case of demyelination was reported in a SIMPONI® I.V.-treated patient (in the PsA trial). Through the

controlled and uncontrolled periods of the SIMPONI® I.V. Phase 3 studies in RA, PsA and AS with a median follow-up of 1.2 years, there were no additional cases of demyelination.

Hepatic

In the controlled period of RA and PsA pivotal trials, mild ALT elevations (>1 and <3 x ULN) occurred in similar proportions of golimumab-treated and control patients (22.1% to 27.4% of patients); in the AS study, more golimumab-treated patients (25.6%) than control patients (3.9%) had mild ALT elevations. With a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in SIMPONI®-treated and control patients. In the AS pivotal trial, the incidence of mild ALT elevations was higher in golimumab-treated patients than in control patients**.** In the controlled period of UC pivotal trials of golimumab induction, mild ALT elevations (>1 and <3 x ULN) occurred in 8.0% and 6.9% of golimumab-treated and control patients, respectively. In the controlled and uncontrolled periods of the UC pivotal trials with a mean follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab and 13.0% in patients receiving placebo.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥5 x ULN were uncommon and seen in more SIMPONI®-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials with a median follow-up of 5 years, ALT elevations ≥5 x ULN were observed in 2.0% (34/1740 patients; 0.81 events per 100 patient years) across the RA studies, 0.8% (3/394 patients; 0.91 events per 100 patient years) for the PsA study and 1.4 % (8/564 patients; 0.61 events per 100 patient years) for the AS studies for the golimumab-treated patients. The majority of these elevations were asymptomatic.

In the controlled periods of the pivotal UC trials of golimumab induction, ALT elevations ≥5 x ULN occurred in 0.3% and 1.0% of golimumab-treated patients and placebo-treated patients, respectively. In the controlled and uncontrolled periods of the Phase 2/3 studies in UC with a mean follow-up of approximately 1 year, the incidence of ALT elevations ≥3 x ULN was 2% in patients receiving SIMPONI® and 0.7% in patients receiving placebo. The incidence of ALT elevations ≥5 x ULN was 0.8% in patients receiving SIMPONI® and 1.2% in patients receiving placebo.

In the controlled Phase 3 trials in RA, PsA and AS through Week 16, the proportions of patients with hepatobiliary adverse events were 0.9% (SIMPONI® 50 mg), 0.7% (SIMPONI® 100 mg) and 0.6% (placebo). At Week 24, the proportions of patients with hepatobiliary adverse events were 0.9% (SIMPONI® 50 mg), 1.3% (SIMPONI® 100 mg) and 0.6% (placebo). In controlled and uncontrolled periods of the Phase 3 studies in RA, PsA and AS through approximately 3 years, 3.5% of SIMPONI®-treated patients had hepatobiliary adverse events.

In the controlled period of the SIMPONI® I.V. Phase 3 trial in RA, through Week 24, mild ALT elevations (>1 and <3 x ULN) occurred in 30.9% of SIMPONI® I.V.-treated patients and 22.8% of placebo-treated patients In the controlled period of the SIMPONI® I.V. Phase 3 trial in PsA through Week 24, mild ALT elevations (>1 and <3 x ULN) occurred in 34.2% of SIMPONI® I.V.-treated patients and 25.9% of placebo-treated patients. In the controlled period of the SIMPONI® I.V. Phase 3 trial in AS through Week 16, mild ALT elevations (>1 and <3 x ULN)

occurred in 27.6% of SIMPONI® I.V.-treated patients and 9.7% of placebo treated patients. Through 1.2 years of follow-up, the incidence of mild ALT elevations across the 3 trials was 107 events/100 patient-years in SIMPONI® I.V.-treated patients compared to the rates for SIMPONI® I.V. in the controlled period which was 172/100 patient-years.

In the controlled period of the SIMPONI® I.V. Phase 3 trial in RA through Week 24, ALT elevations ≥ 3 x ULN to < 5 x ULN occurred in 2.0% of SIMPONI® I.V.-treated patients and 2.5% of placebo-treated patients. In the controlled period of the SIMPONI® I.V. Phase 3 trial in PsA through Week 24, ALT elevations ≥ 3 x ULN to < 5 x ULN occurred in 2.9% of SIMPONI® I.V.-treated patients and 0.4% of placebo-treated patients. In the controlled period of the SIMPONI® I.V. Phase 3 trial in AS trial through Week 16, ALT elevations ≥ 3 x ULN to < 5 x ULN occurred in 0.9% of SIMPONI® I.V.-treated patients and 0% of placebo-treated patients. Through 1.2 years of follow-up, the incidence of ALT elevations ≥3 to <5 x ULN across the 3 trials was 5.7 events/100 patient-years in SIMPONI® I.V.-treated patients, compared to the rate for SIMPONI® I.V. in the controlled period, which was 13/100 patient-years.

In the controlled period of the SIMPONI® I.V. Phase 3 trial in RA through Week 24, ALT elevations ≥5 x ULN were uncommon and seen in 0.8% of SIMPONI® I.V.-treated patients and 0% of placebo-treated patients. In the controlled period of the SIMPONI® I.V. Phase 3 trial in PsA through Week 24, ALT elevations ≥5 x ULN were seen in 1.7% of SIMPONI® I.V.-treated patients and 0.4% of placebo-treated patients. In the controlled period of the SIMPONI® I.V. Phase 3 trial in AS through Week 16, ALT elevations ≥5 x ULN were uncommon and seen in 0% of SIMPONI® I.V.-treated patients and 1.0% of placebo-treated patients. Through 1.2 years of follow-up, the incidence of ALT elevations ≥5 x ULN across the 3 trials was 2.3 events/100 patient-years in SIMPONI®I.V.-treated patients similar to rates for SIMPONI® I.V. in the controlled period, which was 2.8/100 patient-years. The majority of these elevations were asymptomatic.

In the controlled SIMPONI® I.V. Phase 3 trials in RA, PsA and AS, the proportions of patients with hepatobiliary adverse events were 0.4% in SIMPONI® I.V.-treated subjects and 0.2% in placebo-treated subjects. In the controlled and uncontrolled portions of the Phase 3 studies in RA, PsA and AS through 1.2 years, 0.4% of SIMPONI® I.V.- treated patients had hepatobiliary adverse events.

Infections (See **WARNINGS AND PRECAUTIONS, Infections**)
In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab -treated patients (incidence per patient-year: 0.61; 95% confidence interval; CI: 0.55, 0.67) as compared with 10.7% of control patients (incidence per patient-year: 0. 53; 95% CI: 0.44, 0.63). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, upper respiratory tract infections were observed in 46.2% (1693/3666; 0.35 events per patient year) for golimumab-treated patients**.**

In the controlled period of pivotal trials, infections were observed in 22.8% of golimumab-treated patients (incidence per patient-year: 1.30; 95% CI: 1.22, 1.40) compared with 19.9% of control patients (incidence per patient-year: 1.23; 95% CI: 1.09, 1.38). In the controlled and

uncontrolled portions of the studies with a median follow-up of approximately 4 years, infections were observed in 65.5% (2438/3666; 0.81 events per patient year) for golimumab-treated patients. In the controlled Phase 2/3 trials through Week 6 of SIMPONI® induction in UC, infections were observed in 11.9% of SIMPONI®-treated patients compared with 11.3% of control patients. Through week 54 of UC trials, the incidence per patient year of infections was 39% [0.86 events (95% CI: 0.78, 0.94)] in patients receiving SIMPONI® induction and 100 mg maintenance, 44% [1.0 events (95% CI: 0.85, 1.18)] in patients receiving SIMPONI® induction and 50 mg maintenance, and 35% [0.95 events (95% CI: 0.78, 1.15)] in patients receiving SIMPONI® induction and placebo maintenance.

Serious infections observed in golimumab-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections and tuberculosis. In the controlled period of RA, PsA, and AS trials, serious infections were observed in 1.4% of golimumab-treated patients and 1.3% of control-treated patients. The incidence of serious infections per patient-year of follow-up in the controlled period of RA, PsA and AS trials was 0.07 (95% CI:0.05, 0.11) for the golimumab 100 mg group, 0.03 (95% CI: 0.01, 0.07) for the golimumab 50 mg group, and 0.04 (95% CI: 0.02, 0.08) for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per patient-year of all serious infections was 0.04 (95% CI: 0.04, 0.05) in patients receiving golimumab 100 mg and 0.03 (95% CI: 0.02, 0.03) in patients receiving golimumab 50 mg. These results may be confounded by the designs of the Phase 3 studies and different durations of follow-up across treatment groups.

Through week 54 of UC trials, the incidence per patient year of serious infections was 3.3% [0.04 events (95% CI: 0.02, 0.06)] in patients receiving SIMPONI® induction and 100 mg maintenance, 3.2% [0.05 events (95% CI: 0.02, 0.11)] in patients receiving SIMPONI® induction and 50 maintenance, and 2.5% [0.06 events (95% CI: 0.02, 0.12)] in patients receiving SIMPONI® induction and placebo maintenance. Infectious agents include bacterial, mycobacterial, invasive fungal, and other opportunistic infectious agents (see **WARNINGS AND PRECAUTIONS, Infections**). Among 1233 UC patients treated with at least one dose of SIMPONI®, 4 cases of TB and 3 cases of opportunistic infections were reported through Week 54. All opportunistic infections and 3 of 4 TB occurred in patients receiving SIMPONI® at the 100 mg maintenance dose. Among 599 UC patients treated with at least one dose of SIMPONI® during the study extension (Weeks 54 – 228), 4 cases of TB and 3 cases of opportunistic infections were reported in patients receiving SIMPONI® at the 100 mg maintenance dose.

Upper respiratory tract infection was the most common adverse reaction reported in the SIMPONI® I.V. Phase 3 trials in RA, PsA and AS, occurring in 5.3% of SIMPONI® I.V.-treated patients. In controlled SIMPONI® I.V. Phase 3 trials in RA, PsA and AS, infections were observed in 23.8% of SIMPONI® I.V.-treated patients compared with 17.3% of control patients.

Serious infections observed in SIMPONI® I.V. and SIMPONI®-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections, tuberculosis, invasive fungal infections,

and hepatitis B infection. Cases of tuberculosis included pulmonary and extrapulmonary tuberculosis. The overwhelming majority of the tuberculosis cases occurred in countries with a high incidence rate of tuberculosis. No cases of tuberculosis have been reported in 1153 patients treated with SIMPONI® I.V. or SIMPONI® in the United States and Canada in the Phase 2 RA and Phase 3 RA, PsA, AS and IV RA trials with 2544 patient-years of follow-up.

In controlled SIMPONI® I.V. Phase 3 trials in RA, PsA and AS, serious infections were observed in 0.8% of SIMPONI® I.V.-treated patients and 0.4% of control-treated patients. The incidence of serious infections per 100 patient-years of follow-up was 1.9 (95% CI: 0.7, 4.1) for the SIMPONI® I.V.-treated patients, and 0.9 (95% CI: 0.1, 3.3) for the placebo-treated patients.

In the controlled and uncontrolled portions of the Phase 3 IV trials in RA, PsA and AS representing 1265 total patient-years of follow-up with a median follow-up of 1.2 years, the incidence per 100 patient-years of all serious infections was 3.6 (95% CI: 2.6, 4.8) in patients receiving SIMPONI® I.V. The incidence of active tuberculosis per 100 patient-years was 0.20 (95% CI: 0.0, 0.6) in patients receiving SIMPONI® I.V. The incidence of other opportunistic infections per 100 patient-years was 0.2 (95% CI: 0.0, 0.7) in patients receiving SIMPONI® I.V.

Immune

Autoantibodies

Use of TNF-blocking agents has been associated with the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.

In the controlled and uncontrolled periods of the pivotal trials through 1 year of follow up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titers of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow up in patients anti-dsDNA negative at baseline was 1.1%.

In Phase 2/3 trials in UC through approximately 1 year of follow up, 3.5% of patients who received SIMPONI® induction and 100 mg during the maintenance portion of the UC studies**,** 4.8% of patients who received SIMPONI® induction and 50 mg during the maintenance portion of the UC studies, and 3.5% of patients who received SIMPONI® induction and placebo during the maintenance portion of the UC studies were newly ANA-positive (at titers of 1:160 or greater). The frequency of anti-ds DNA antibodies at 1 year of follow up in patients who were anti-dsDNA negative at baseline was 3 (0.5%) in patients receiving SIMPONI® induction and 100 mg during maintenance, 1 (0.7%) in patients receiving SIMPONI® induction and 50 mg during maintenance and 0 (0%) in patients who received SIMPONI® induction and placebo during maintenance.

In the controlled period of the SIMPONI® I.V. trial in RA through Week 20, 17% of SIMPONI® I.V.-treated patients and 15% of control patients were newly Anti-Nuclear Antibody (ANA)-positive. Of these patients, no SIMPONI® I.V.-treated patient or control-treated patient was newly positive for anti-dsDNA antibodies. In the controlled period of the SIMPONI® I.V. trial in PsA through Week 16, 8% of SIMPONI® I.V.-treated patients and 17% of control patients were newly ANA-positive. Of these patients, 1 SIMPONI® I.V.-treated patient and no control-treated patient were newly positive for anti-dsDNA antibodies. In the controlled period of the

SIMPONI® I.V. trial in AS through Week 16, 8% of SIMPONI® I.V.-treated patients and 5% of control patients were newly ANA-positive. Of these patients, no SIMPONI® I.V.-treated patient or control-treated patient had newly positive anti-dsDNA antibodies through 16 weeks of follow-up.

Immunogenicity

Following SC administration in patients with RA, PsA or AS, antibodies to SIMPONI®, nearly all neutralizing *in vitro*, were detected by the enzyme immunoassay (EIA) method in 5% of SIMPONI®-treated patients through Week 52. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to SIMPONI® than patients receiving SIMPONI® without MTX (approximately 3% versus 8%, respectively).

Following SC administration in patients with nr-Ax SpA, antibodies to SIMPONI®, all neutralizing *in vitro*, were detected in 4% of SIMPONI®-treated patients through Week 16 by the EIA method.

Following SC administration in UC patients, antibodies to SIMPONI® were detected by the EIA method in 34 (2.7%) of SIMPONI®-treated patients through Week 54. 21 (68%) of antibody-positive patients had neutralizing antibodies in vitro. The proportion of patients achieving clinical response was 22% (2/9) in antibody-positive patients compared with 51% (148/290) antibody-negative patients. Median serum golimumab concentrations were lower in antibody-positive subjects compared with levels in antibody-negative subjects. The model-predicted mean clearance (CL) value for golimumab was 24.3% higher in antibody-positive patients compared with antibody-negative patients. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to SIMPONI® than patients receiving SIMPONI® without immunomodulators (1.3% versus 3.4%, respectively).

Following administration of SIMPONI® I.V. in combination with MTX in RA patients, antibodies to golimumab were detected by the EIA method in 4.2% (39/922) of golimumab-treated patients through approximately 1 year. All patients who were positive for antibodies to golimumab had neutralizing antibodies *in vitro*.

The small number of patients positive for antibodies to golimumab detected by the EIA method limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to golimumab in an EIA assay.

A drug-tolerant EIA method was subsequently developed for the detection of antibodies to golimumab. This method is approximately 16-fold more sensitive than the original EIA method with less interference from golimumab in serum. Due to the higher sensitivity and the improved drug tolerance, a higher incidence of antibodies to golimumab was expected to be detected with the drug-tolerant EIA method compared to the original EIA method.

Following IV administration in patients with RA, PsA or AS, antibodies to SIMPONI® I.V. were detected using the drug-tolerant EIA in 20% of SIMPONI® I.V. -treated patients (RA: 21%, PsA: 19%, and AS: 19%). Where tested, approximately one-third of the antibodies to SIMPONI® I.V. were neutralizing. Treatment with concomitant MTX resulted in a slightly lower proportion of patients with antibodies to SIMPONI® I.V. than patients receiving SIMPONI® I.V. without MTX (approximately 19% vs. 25%, respectively).
The higher incidence of antibodies to golimumab with the drug-tolerant EIA method were mostly due to low titer antibodies, which did not have an apparent impact on drug concentrations, efficacy and safety. Although higher-titer antibodies, which were mostly neutralizing, may be associated with lower drug concentrations and diminished efficacy, there were few patients with high titers in the IV PsA and IV AS studies. Development of antibodies to SIMPONI® I.V. did not preclude clinical response.

The observed incidence of antibody positivity may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, underlying disease, and particularly the sensitivity of the assay. For these reasons, comparison of the incidence of antibodies to SIMPONI® I.V. with the incidence of antibodies to other products or results from different assays may be misleading.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Adverse drug reactions that occurred at rates less than 1% during the SIMPONI® and SIMPONI® I.V. clinical trials included the following events listed by system organ class:

Blood and lymphatic disorders: thrombocytopenia, pancytopenia

Cardiac disorders: congestive heart failure (new onset or worsening)

Infections and infestations: sepsis including septic shock, tuberculosis, histoplasmosis, coccidioidomycosis, pneumocystosis, opportunistic infections (invasive fungal infections, bacterial, atypical mycobacterial and protozoal), arthritis bacterial, pyelonephritis, bursitis infective, and hepatitis B reactivation (See **WARNINGS AND PRECAUTIONS, Infections,** Opportunistic Infections)

Musculoskeletal and connective tissue disorders: lupus-like syndrome

Neoplasm benign and malignant: Lymphoma, pediatric malignancy, leukemia

Nervous system disorders: demyelinating disorders (central and peripheral)

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: psoriasis: new onset or worsening, palmar/plantar, and pustular, vasculitis (cutaneous)

Vascular disorders: vasculitis (systemic)

Post-Market Adverse Drug Reactions

Adverse reactions have been reported from worldwide post-marketing use of SIMPONI®/SIMPONI® I.V. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to SIMPONI®/SIMPONI® I.V. exposure.

General Disorders and Administration Site Conditions: Infusion-related reaction.

Immune system disorders: serious systemic hypersensitivity reactions (including anaphylactic reaction), sarcoidosis

Neoplasm benign and malignant: melanoma, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma (HSTCL)*

Skin and subcutaneous tissue disorders: bullous skin reactions, skin exfoliation

*observed with other TNF-blocking agents

DRUG INTERACTIONS

Overview

SIMPONI® can be used in combination with methotrexate in adult patients with RA, AS or PsA. Specific drug interaction studies have not been conducted with SIMPONI®.

For patients with RA, SIMPONI® I.V. should be used in combination with methotrexate (MTX). For patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS), SIMPONI® I.V. may be given with or without MTX or other non-biologic disease-modifying antirheumatic drugs (DMARDs). Corticosteroids, nonsteroidal anti-inflammatory drugs NSAIDs and/or analgesics may be continued during treatment with SIMPONI® I.V. Specific drug interaction studies have not been conducted with SIMPONI® I.V.

Drug-Drug Interactions

Concurrent Use of SIMPONI®/SIMPONI® I.V. with other Biological Therapeutics
The combination of SIMPONI® with other biological therapeutics used to treat the same conditions as SIMPONI®/SIMPONI® I.V., including anakinra or abatacept is not recommended (see **WARNINGS and PRECAUTIONS).**

Live Vaccines/Therapeutic Infectious Agents
Live vaccines should not be given concurrently with SIMPONI®/SIMPONI® I.V. (see **WARNINGS and PRECAUTIONS, Immune,** Immunizations).

Therapeutic infectious agents should not be given concurrently with SIMPONI®/SIMPONI® I.V.

Methotrexate

Although concomitant use of methotrexate (MTX) results in higher steady-state trough concentrations of SIMPONI® and reduction of its apparent clearance (approximately by 36%) in patients with RA, PsA, or AS, the data do not suggest the need for dose adjustment of either SIMPONI® or methotrexate (see **Pharmacokinetics**).

SIMPONI® I.V. should be used with MTX for the treatment of RA. No significant effect of MTX on the clearance of SIMPONI® I.V. was observed. SIMPONI® I.V. may be used with or without MTX for the treatment of PsA or AS. Population PK analysis indicated that concomitant use of MTX did not significantly influence the clearance of golimumab.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI®/SIMPONI® I.V. in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Drug-Herb Interactions

Interactions with herbal products have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

SIMPONI®

SIMPONI® is intended for use under the guidance and supervision of a physician. After an initial training in proper subcutaneous injection technique, an adult patient with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or ulcerative colitis may self-inject with SIMPONI® if a physician determines that it is appropriate and with medical follow-up as necessary.

At the time of dosing, if multiple injections are required, the injections should be administered at different sites on the body.

Comprehensive instructions for the administration of SIMPONI® are given in ***PART III: CONSUMER INFORMATION*, PROPER USE OF THIS MEDICATION** for preparation and giving an injection of SIMPONI®. Patients should be instructed to inject the full amount of SIMPONI® according to the directions provided in the ***CONSUMER INFORMATION***.

SIMPONI® I.V.

Intravenous infusion of SIMPONI® I.V. should be administered by qualified health care professionals trained to detect any infusion-related issues.

See **Administration** section for comprehensive instructions for the intravenous infusion of SIMPONI® I.V.

Recommended Dose and Dosage Adjustment

SIMPONI®

SIMPONI® is administered by subcutaneous injection.

Adult Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis Patients
50 mg of SIMPONI® given as a subcutaneous injection once a month, on the same date each month.

For all the above indications, available data from clinical trials suggest that clinical response is usually achieved within 14 to 16 weeks of treatment (after 4 doses). Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Data from clinical trials for RA and PsA suggest that efficacy does not increase with doses higher than 50 mg. Doses higher than 50 mg have not been studied in nr-Ax SpA.

Adult Ulcerative Colitis
200 mg initially administered by subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 50 mg every 4 weeks, thereafter.

The maintenance dose of 100 mg every 4 weeks can be considered at the discretion of the treating physician. In addition to the clinical assessment, measurement of golimumab levels may be taken into account before considering dose optimization as some patients may not benefit from dose escalation.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Missed Dose

Patients who miss a dose of SIMPONI®, should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose (see ***Part III: CONSUMER INFORMATION,*** **PROPER USE OF THIS MEDICATION,** autoinjector and pre-filled syringe).

SIMPONI® I.V.

SIMPONI® I.V. is administered by intravenous infusion.

Adult Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis Patients
2 mg/kg of SIMPONI® I.V. given as a 30-minute intravenous infusion at Weeks 0 and 4, then every 8 weeks thereafter.

The efficacy and safety of switching between intravenous and subcutaneous formulations and routes of administration have not been established.

Special Populations

Geriatrics
Pharmacokinetic parameters including apparent clearance were not influenced by age in SIMPONI®/ SIMPONI® I.V. clinical trials. Dose adjustment is not required in elderly patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics
The safety and efficacy of SIMPONI®/ SIMPONI® I.V. have not been established in pediatric patients aged 17 years and younger.

Renal impairment
Specific studies of SIMPONI®/ SIMPONI® I.V. have not been conducted in patients with renal impairment.

Hepatic impairment
Specific studies of SIMPONI®/ SIMPONI® I.V. have not been conducted in patients with hepatic impairment. SIMPONI® / SIMPONI® I.V. should be used with caution in subject with impaired hepatic function.

Administration

SIMPONI®

SIMPONI® is supplied as a single-use, sterile solution in a pre-filled syringe and single-use autoinjector administered by subcutaneous injection (see **Dosing Considerations**).

SIMPONI® I.V.

SIMPONI® I.V. is supplied as a sterile solution for intravenous infusion (see **Dosing Considerations**).

Use aseptic technique.

1. Calculate the dose and the number of SIMPONI® I.V. vials needed based on patient weight. Each 4 mL vial of SIMPONI® I.V. contains 50 mg of golimumab.

2. Check that the solution is colourless to light yellow. The solution may develop a few fine translucent particles, as golimumab is a protein. Do not use if opaque particles, discoloration or other foreign particles are present.

3. Dilute the total volume of the SIMPONI® I.V. solution dose to 100 mL with 0.9% w/v sodium chloride for infusion. This can be accomplished by withdrawing a volume of the 0.9% w/v sodium chloride solution from the 100 mL glass bottle or infusion bag equal to the volume of SIMPONI® I.V. and discarding the withdrawn solution. Alternatively, SIMPONI® I.V. can be diluted using the same method described above with 0.45% w/v sodium chloride for infusion.

4. Slowly add the total volume of SIMPONI® I.V. solution to the 100-mL infusion bottle or bag. Gently mix.

5. Prior to infusion, visually inspect parenteral medicinal products for particulate matter or discoloration. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.22 micrometre or less). Do not store any unused portion of the infusion solution for reuse.

7. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of SIMPONI® I.V. with other agents. Do not infuse SIMPONI® I.V. concomitantly in the same intravenous line with other agents.

8. Infuse the diluted solution over a period of 30 +/- 10 minutes. The infusion of the diluted solution should be completed within 6 hours after preparation.

9. Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

The maximum tolerated dose of golimumab has not been established in humans. Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF, which prevents the binding of TNF to its receptors. No binding to other TNF super-family ligands was observed; in particular, golimumab does not bind or neutralize human lymphotoxin. TNFα is synthesized primarily by activated monocytes, macrophages and T-cells as a transmembrane protein that self-associates to form the bioactive homotrimer and is rapidly released from the cell surface by proteolysis. The binding of TNF to either the p55 or p75 TNF receptors leads to the clustering of the receptor cytoplasmic domains and initiates signaling.[1,2] TNF has been identified as a key sentinel cytokine that is produced in response to various stimuli and subsequently promotes the inflammatory response through activation of the caspase-dependent apoptosis pathway and the transcription factors nuclear factor (NF)-κB and activator protein-1 (AP-1).[1,2] TNF also modulates the immune response through its role in the organization of immune cells in germinal centres.[3] Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis, as well as spondyloarthropathies such as psoriatic arthritis and ankylosing spondylitis, and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.[4,5,6,7]

Pharmacodynamics

Nonclinical

The binding of human TNF by golimumab was shown to neutralize TNF-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab. Consistent with other human IgG1 antibodies, golimumab is capable of binding to Fc receptors and activating complement.

However, no golimumab-mediated cell lysis was seen with lipopolysaccharide (LPS)-stimulated human monocytes upon addition of complement or effector cells. In addition, no golimumab-induced apoptosis was detected with LPS-stimulated human peripheral blood mononuclear cells. The effect of golimumab *in vivo* was tested in a human TNF transgenic mouse model of experimental arthritis. Golimumab treatment produced a statistically significant delay in the onset of clinical symptoms compared with untreated mice, as well as a significant reduction in joint pathology.

Clinical

SIMPONI® was effective in modulating select markers of inflammation and bone metabolism across indications. Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with SIMPONI® resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNFα were significantly reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients.

These changes were observed at the first assessment (Week 4) after the initial SIMPONI® administration and were generally sustained through Weeks 14 and/or 24. SIMPONI® with or without methotrexate (MTX) resulted in significant changes in serum levels of select markers of bone metabolism [increases in osteocalcin and procollagen type I N-terminal propeptide (PINP) and decreases in deoxy-pyridinoline (DPD) levels] at Week 4. All of these biomarker changes are consistent with an improvement in the disease processes with reduced inflammation, increased bone growth and decreased bone resorption.

Following treatment with SIMPONI® I.V. in patients with RA, decreases from baseline were observed in tissue inhibitor of metalloproteinases 1 (TIMP-1), matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-3 (MMP-3), resistin, interleukin-6 (IL-6), macrophage inflammatory protein-1 (MIP-1b), vascular endothelial growth factor (VEGF), serum amyloid A (SAA), S100A12, and high sensitivity C-Reactive protein (hsCRP). Conversely, increases from baseline were observed in abstract tartrate-resistant acid phosphatase (TRAP-5b).

Pharmacokinetics

SIMPONI®

Following SC administration of SIMPONI® to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. The systemic clearance of SIMPONI® was estimated to be 6.9 ± 2.0 mL/day/kg, and mean volume of distribution 115 ± 19 mL/kg in healthy subjects; in patients with RA, the systemic clearance of SIMPONI® was estimated to be 7.6 ± 2.0 mL/day/kg, and mean volume of distribution 151.1 ± 61mL/kg. The volume of distribution for SIMPONI® indicates that SIMPONI® is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be approximately 2 weeks in healthy subjects and patients with RA, PsA, AS, or UC. Following SC administration of SIMPONI® in healthy subjects, the following PK parameters were obtained as shown in Table 4.

TABLE 4: Pharmacokinetic parameters of SIMPONI® following a single subcutaneous injection of SIMPONI® in healthy subjects

Pharmacokinetic Parameter	SIMPONI® 50 mg (n=26)	SIMPONI® 100 mg (n=266)
Maximum observed serum concentration (C_{max}, μg/mL)	2.7 ± 0.9	6.3 ± 2.9
Time to reach C_{max} (T_{max}, day)[a]	5 (2, 10)	4 (1, 10)
Area under the curve from time 0 to infinity (AUC_{inf}, μg·day/mL)	49.4 ± 15.3	99.7 ± 40.1
Terminal half-life ($T_{1/2}$, day)	11 ± 3	12 ± 3
Apparent systemic clearance (CL/F, mL/day/kg)	17.1 ± 9.0	14.8 ± 5.9

TABLE 4: Pharmacokinetic parameters of SIMPONI® following a single subcutaneous injection of SIMPONI® in healthy subjects

Pharmacokinetic Parameter	SIMPONI® 50 mg (n=26)	SIMPONI® 100 mg (n=266)
Apparent volume of distribution (V_z/F, mL/kg)	252 ± 71	241 ± 100

[a]Mean ± SD values are shown for all PK parameters except for T_{max} which is presented as the median value with the range of minimum and maximum.

Following a single IV dose in patients with RA, SIMPONI® exhibited dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg. Following a single SC dose in healthy subjects, dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg with both C_{max} and area under the concentration-time curve (AUC) increased proportionally.

Following a single SC injection of 100 mg, the absorption of SIMPONI® was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since SIMPONI® exhibited approximately dose proportional PK following SC administration, the absolute bioavailability of the SIMPONI® 50 mg or 200 mg dose is expected to be similar to the 100 mg dose.

When 50 mg SIMPONI® was administered SC to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by Week 12. With concomitant use of methotrexate, treatment with 50 mg SIMPONI® every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 µg/mL in patients with active RA despite methotrexate therapy, and approximately 0.5 µg/mL in patients with active PsA and approximately 0.6 µg/mL in patients with AS. Patients with RA, PsA or AS who did not receive concomitant use of methotrexate had approximately 30% lower steady-state trough concentrations of SIMPONI® than those who received SIMPONI® with methotrexate. Concomitant use of methotrexate reduced the apparent clearance of SIMPONI® by 36% after 6-month treatment with SIMPONI® in patients with RA. However, population PK analysis indicated that concomitant use of nonsteroidal anti-inflammatory drugs, oral corticosteroids or sulfasalazine was not found to influence the apparent clearance of SIMPONI®.

Steady-state mean trough serum golimumab concentrations in patients with nr-Ax SpA were comparable to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 week.

Following induction doses of 200 mg and 100 mg SIMPONI® at Week 0 and 2 respectively, and maintenance doses of 100 mg SIMPONI® every 4 weeks thereafter in patients with UC, serum golimumab concentrations reached steady-state approximately 14 weeks after the start of therapy. Treatment with 100 mg SIMPONI® every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 1.8 ± 1.1 µg/mL.

Population pharmacokinetic analyses showed there was a trend toward higher apparent clearance of SIMPONI® with increasing weight. As a result, patients with heavier weight tend to have lower steady-state trough concentrations of SIMPONI®. However, across the RA, PsA, and AS populations, a treatment benefit from golimumab 50 mg was observed for all subgroups by weight quartiles with no meaningful differences in clinical efficacy among these subgroups. Treatment with the recommended dose regimens of SIMPONI® in UC patients did not result in meaningful differences in clinical efficacy among the different weight subgroups, particularly among patients receiving the 100 mg maintenance dose. Therefore, there is no need to adjust the dosage of SIMPONI® based on a patient's weight.

No gender-related pharmacokinetic differences were observed with SIMPONI® after correction for patients' body weights. Pharmacokinetic parameters of SIMPONI® were not influenced by age in adult patients. Patients with age ≥65 years had apparent clearance of SIMPONI® similar to patients with age <65 years. No ethnicity-related pharmacokinetic differences were observed between Caucasians and Asians.

Patients who developed anti-SIMPONI® antibodies generally had low trough steady-state serum concentrations of SIMPONI®.

SIMPONI® I.V.

Absorption
Following a single IV administration of 2 mg/kg SIMPONI® I.V., a mean C_{max} of 44.4 ±11.3 μg/mL was observed in patients with RA.

Distribution
Following a single IV administration of 2 mg/kg SIMPONI® I.V., the mean volume of distribution was estimated to be 115 ± 19 mL/kg in healthy subjects, and 151 ± 61 mL/kg in patients with RA. The volume of distribution of golimumab indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Elimination
The elimination pathways for golimumab have not been characterized.

Following a single IV administration of 2 mg/kg SIMPONI® I.V., the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg in healthy subjects and 7.6 ± 2.0 mL/day/kg in patients with RA. The mean terminal half-life was estimated to be 12 ± 3 days in healthy subjects and the mean terminal half-life in RA patients was 14 ± 4 days.

In RA, PsA and AS, population PK analysis indicated that concomitant use of MTX, NSAIDs, oral corticosteroids, or sulfasalazine (SSZ) did not significantly influence the clearance of golimumab following IV administration.

When 2 mg/kg SIMPONI® I.V. was administered IV to patients with RA at weeks 0, 4 and every 8 weeks thereafter, serum concentrations reached steady state by Week 12. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state

trough serum concentration of approximately 0.4 ± 0.4 μg/mL in patients with active RA. The mean steady-state trough serum concentration in patients with PsA was 0.7 ± 0.6 μg/mL. The mean steady-state trough serum concentration in patients with AS was 0.8 ± 0.6 μg /mL.

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab.

No formal study of the effect of renal or hepatic impairment on the PK of golimumab was conducted.

Dose Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single IV dose.

Effect of weight on pharmacokinetics
Following IV administration, patients with higher body weights tended to have slightly higher serum golimumab concentrations than patients with lower body weights when golimumab was administered on a mg/kg (body weight) basis. However, based on population PK analysis, there were no clinically relevant differences in golimumab exposure following IV administration of 2 mg/kg SIMPONI® I.V. in patients across a range of different body weights.

Special Populations and Conditions

Pediatrics: The safety and efficacy of SIMPONI®/ SIMPONI® I.V. have not been established in pediatric patients aged 17 years and younger.

Geriatrics: Pharmacokinetic parameters of SIMPONI®/SIMPONI® I.V. were not influenced by age in adult patients. Patients with age ≥65 years had apparent clearance of SIMPONI®/SIMPONI® I.V. similar to patients with age <65 years.

Gender: No gender-related pharmacokinetic differences were observed with SIMPONI®/SIMPONI® I.V. after correction for patients' body weights.

Race: No ethnicity-related pharmacokinetic differences were observed between Caucasians and Asians.

Hepatic insufficiency: SIMPONI®/SIMPONI® I.V. has not been studied in this patient population. No dose recommendation can be made.

Renal insufficiency: SIMPONI®/SIMPONI® I.V. has not been studied in this patient population. No dose recommendation can be made.

STORAGE AND STABILITY

Store SIMPONI®/SIMPONI® I.V. refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Keep the product in original carton until time of use to protect from light. Do not freeze. Do not shake.

SIMPONI®/SIMPONI® I.V. may be stored at room temperature up to a maximum of 25°C (77 ºF) for a single period of up to 30 days in the original carton; after which, it should not be refrigerated again. Once removed from refrigerated storage, the room temperature expiration date should be written on the carton. SIMPONI®/SIMPONI® I.V. must be protected from light.

Keep out of the sight and reach of children.

Once the SIMPONI® I.V. solution has been diluted, it should be stored at room temperature, protected from light and the infusion should be completed within 6 hours of preparation.

SPECIAL HANDLING INSTRUCTIONS

SIMPONI®

See ***PART III: CONSUMER INFORMATION*, PROPER USE OF THIS MEDICATION** for comprehensive instructions for the use, handling, and disposal of the autoinjector and the pre-filled syringe.

SIMPONI® I.V.

See **DOSAGE AND ADMINISTRATION, Administration**, for comprehensive instructions for the use, handling, and disposal of the vial.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SIMPONI®

SIMPONI® is supplied as a single-use, sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. The syringe is contained in a single-use autoinjector or fitted with a passive safety guard. The syringe is stoppered with a coated stopper and the needle is covered with a needle shield to prevent leakage of the solution through the needle and to protect the needle during handling prior to administration. The fixed needle is a 5-bevel, 27G, half-inch stainless steel needle. The needle shields are manufactured using a dry natural rubber containing latex (See **WARNINGS AND PRECAUTIONS, Allergic Reactions**, Latex Sensitivity).

Each mL of SIMPONI® contains 100 mg of golimumab, 0.87 mg L-histidine and L-histidine hydrochloride, 41.0 mg sorbitol, 0.15 mg polysorbate 80, and water for injection. SIMPONI® is available in two strengths: 50 mg of golimumab in 0.5 mL and 100 mg of golimumab in 1 mL.

Autoinjector:

- Each 50 mg single-use autoinjector contains 50 mg golimumab per 0.5 mL in an autoinjector.
- Each 100 mg single-use autoinjector contains 100 mg golimumab per 1 mL in an autoinjector.

SIMPONI® is supplied as a sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. This syringe is contained in a single-use autoinjector. The needle shields are manufactured from dry natural rubber containing latex (see **WARNINGS AND PRECAUTIONS, Allergic Reactions**, Latex Sensitivity). SIMPONI® is available in packs of 1 autoinjector.

Pre-filled Syringe:

- Each 50 mg single-use pre-filled syringe contains 50 mg golimumab per 0.5 mL syringe.
- Each 100 mg single-use pre-filled syringe contains 100 mg golimumab per 1 mL syringe.

SIMPONI® is supplied as a sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. The needle shields are manufactured from dry natural rubber containing latex (see **WARNINGS AND PRECAUTIONS**, **Allergic Reactions**, Latex Sensitivity).

SIMPONI® is available in packs of 1 pre-filled syringe.

SIMPONI® is packaged in a single-use outer carton.

SIMPONI® I.V.
SIMPONI® I.V. is supplied as a sterile solution for intravenous infusion in a 4 mL single-use vial (50 mg, 12.5 mg/mL).

SIMPONI® I.V. does not contain preservatives. The solution is colorless to light yellow with a pH of approximately 5.5. Each 4 mL vial of SIMPONI® I.V. contains 50 mg golimumab, 1.14 mg L-histidine and 6.42 mg L-histidine monohydrochloride monohydrate, 180 mg sorbitol, 0.6 mg polysorbate 80, and water for injection.

SIMPONI® I.V. is packaged in a single-use outer carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

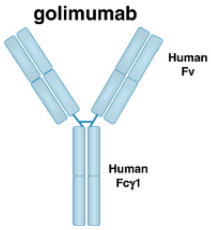
Proper name: golimumab

Chemical name: Not applicable. Golimumab is not a chemical. Golimumab is a human IgG1κ monoclonal antibody.

Molecular formula and molecular mass:

Golimumab is a human IgG1κ monoclonal antibody that exhibits multiple glycoforms with predicted molecular masses ranging from 149,802 daltons to 151,064 daltons.

Structural formula:



Physicochemical properties: SIMPONI® does not contain preservatives. The solution is clear to slightly opalescent, colourless to light yellow with a pH of approximately 5.5. Each mL of SIMPONI® contains 100 mg of golimumab, 0.87 mg L-histidine and L-histidine hydrochloride, 41.0 mg sorbitol, 0.15 mg polysorbate 80, and water for injection. SIMPONI® is available in two strengths: 50 mg of golimumab in 0.5 mL and 100 mg of golimumab in 1 mL. SIMPONI® I.V. does not contain preservatives. The solution is clear, colourless to light yellow with a pH of approximately 5.5.

Product Characteristics

SIMPONI®/SIMPONI® I.V. is a human IgG1κ monoclonal antibody that exhibits multiple glycoforms with predicted molecular masses ranging from 149,802 daltons to 151,064 daltons. SIMPONI®/SIMPONI® I.V. is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

CLINICAL TRIALS

SIMPONI®

Rheumatoid Arthritis

Study demographics and trial design

The efficacy and safety of SIMPONI® were evaluated in three multicentre, randomized, double-blind, placebo-controlled studies in over 1,500 patients ≥18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening (Table 5). Patients had at least 4 swollen and 4 tender joints. SIMPONI® was administered subcutaneously at doses of 50 mg or 100 mg, with or without MTX, every 4 weeks.

TABLE 5: Summary of controlled clinical trials supporting safety and efficacy in patients with RA

Study #	Trial Design	Dosage: Route of Administration and Duration[a]	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
RA Study 1 (GO-FORWARD)	Multicentre, double-blinded, randomized, placebo-controlled	SIMPONI® 50 mg or 100 mg; sc; q4w for up to 24 weeks			
		SIMPONI® Placebo	311 133	50.4±11.36 (18, 79)	80.6%
RA Study 2 (GO-AFTER)	Multicentre, double-blinded, randomized, placebo-controlled	SIMPONI® 50 mg or 100 mg; sc; q4w for up to 24 weeks			
		SIMPONI® Placebo	295 150	54.1±12.27 (23, 83)	79.6%
RA Study 3 (GO-BEFORE)	Multicentre, double-blinded, randomized, placebo-controlled	SIMPONI® 50 mg or 100 mg; sc; q4w for up to 52 weeks			
		SIMPONI® Placebo	477 160	49.5 ±12.28 (18, 85)	82.9%

[a]Duration of controlled period

RA Study 1 (GO-FORWARD): Active Rheumatoid Arthritis Despite MTX

Study RA-1 (GO-FORWARD) evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomized to receive placebo + MTX (n=133), SIMPONI® 50 mg + MTX (n=89), SIMPONI® 100 mg + MTX (n=89) or SIMPONI® 100 mg monotherapy + placebo (n=133). The co-primary endpoints were the percent of patients achieving ACR 20 response at Week 14 and improvement from baseline in HAQ at Week 24. Major secondary endpoints included change from baseline in van der Heijde-modified Sharp (vdH-S) score at Week 24,

DAS 28 (using CRP) response at Week 14, ACR 20 response at Week 24, and improvement from baseline in HAQ at Week 14. All patients receiving placebo + MTX received SIMPONI® 50 mg + MTX after Week 24, but the trial remained blinded until all patients had completed 52 weeks of treatment. At Week 52, patients entered the long-term extension phase and patients receiving SIMPONI® 50 mg could have the dose increased to 100 mg at the discretion of the investigator. Through Week 252, the time point for the last scheduled study agent administration, 131 (29.5%) treated subjects discontinued study agent. Efficacy data were collected and analyzed through Week 256. Through Week 252, the time point for the last scheduled study agent administration, 29 (32.6%) treated subjects initially randomized to receive golimumab 50 mg, continually received the authorized dose of golimumab 50 mg once a month.

RA Study 2 (GO-AFTER): Active Rheumatoid Arthritis, previously treated with anti-TNFα agent(s)

Study RA-2 (GO-AFTER) evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab, without serious adverse reaction. Reasons for discontinuation of prior anti-TNF therapies included lack of efficacy (59%), intolerance (17%), and/or reasons other than safety or efficacy (39%). Patients were randomized to receive placebo (n=150), SIMPONI® 50 mg (n=147), and SIMPONI® 100 mg (n=148). Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The use of other DMARDs including cytotoxic agents or other biologics was prohibited. The primary endpoint was the percent of patients achieving ACR 20 response at Week 14. Major secondary endpoints included ACR 50 response at Week 14, DAS 28 (using CRP) response at Week 14, ACR 20 response at Week 24 and improvement from baseline in HAQ score at Week 24. Through Week 252, the time point for the last scheduled study agent administration, 276 (60.1%) treated subjects discontinued study agent. Efficacy data were collected and analyzed through Week 256. Through Week 252, the time point for the last scheduled study agent administration, 21 (14.3%) treated subjects initially randomized to receive golimumab 50 mg continually received the authorized dose of golimumab 50 mg once a month.

RA Study 3 (GO-BEFORE): Active Rheumatoid Arthritis, MTX Naïve

Study RA-3 (GO-BEFORE) evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomized to receive placebo + MTX (n=160), SIMPONI® 50 mg + MTX (n=159), SIMPONI® 100 mg + MTX (n=159) or SIMPONI® 100 mg monotherapy + placebo (n=159). For patients receiving active MTX, MTX was administered at a dose of 10 mg/week beginning at Week 0 and increased to 20 mg/week by Week 8. The co-primary endpoints were the percent of patients achieving ACR 50 response at Week 24, and the change from baseline in vdH-S score at Week 52. Major secondary endpoints included the change from baseline in HAQ at Week 52, ACR 20 response at Week 24, the change from baseline in vdH-S score at Week 52 in subjects with abnormal CRP at baseline, and the percent of patients with abnormal CRP at baseline achieving an ACR 50 response at Week 24. At Week 52, patients entered the long-term extension phase in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to SIMPONI® 50 mg + MTX. Patients receiving SIMPONI® 50 mg could have the dose increased to 100 mg at the discretion of the investigator. Through Week 252, the time point for the last scheduled study agent administration, 215 (33.9%) treated subjects discontinued study agent.

Efficacy data were collected and analyzed through Week 256. Through Week 252, 62 (39%) treated subjects initially randomized to receive golimumab 50 mg, continually received the authorized dose of golimumab 50 mg once a month.

Study results

Reduction in Signs and Symptoms

In general, no clinically meaningful differences across efficacy measures were apparent between the SIMPONI® 50 mg and 100 mg dosing regimens in each of the Phase 3 RA studies. Patients in the long-term extension may have their dose modified at the discretion of the study physician.

RA Study 1 (GO-FORWARD)

Treatment with SIMPONI® in patients with active RA despite MTX resulted in improvement in signs and symptoms as demonstrated by the percent of patients achieving an ACR 20 response at Week 14. A significantly greater percent of patients achieved an ACR 20 response in the SIMPONI® 50 mg + MTX group than in the placebo + MTX group ($p \leq 0.001$) at Weeks 14 and 24. The percent of patients achieving ACR 50 and ACR 70 responses was also greater in the SIMPONI® 50 mg + MTX group than in the placebo + MTX group at Weeks 14 and 24 (Table 6).

When ACR 20 responses over time were considered, improvement was observed at the first assessment (Week 4) after the first SIMPONI® 50 mg + MTX administration, and was maintained through Week 24 (Figure 1).

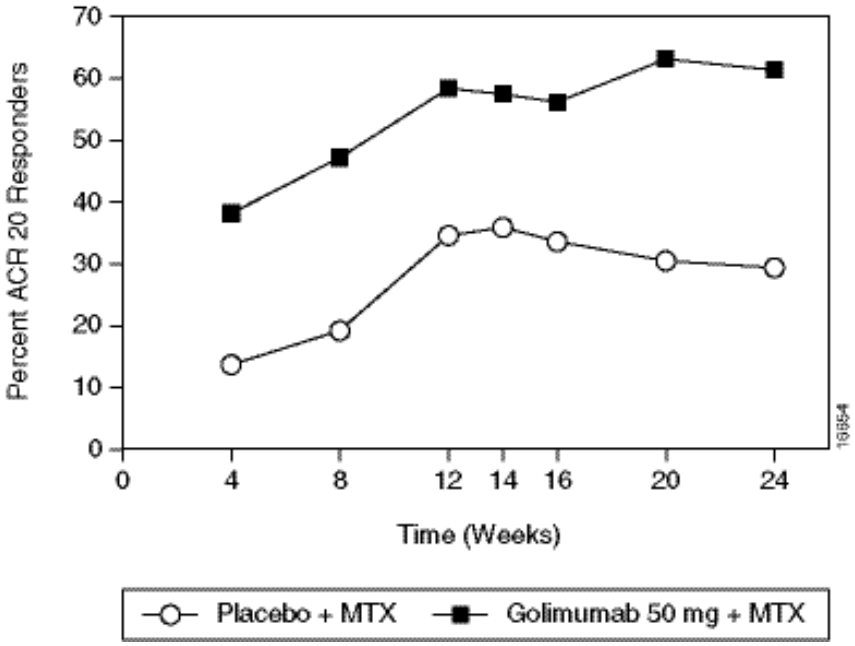


Figure 1: RA Study 1: Percent of patients achieving ACR 20 response through Week 24; randomized patients in placebo + MTX and SIMPONI® 50 mg + MTX dose groups

The percentages of patients achieving a DAS 28 response were 72% and 73% for patients treated with SIMPONI® 50 mg + MTX at Week 14 and at Week 24, respectively, compared to 50% and 42% in those who received placebo + MTX. Remission (defined as DAS28 <2.6) was achieved by 27% of patients treated with SIMPONI® 50 mg + MTX and 7% of those who received placebo + MTX at Week 24.

TABLE 6: RA Study 1: Percent of RA patients with ACR responses at Week 14 and Week 24

	Placebo + MTX (N=133)[a]	**SIMPONI® 50 mg + MTX * (N=89)[a]**
ACR 20 (% responders)		
Week 14	33%	55%
Week 24	28%	60%
ACR 50 (% responders)		
Week 14	10%	35%
Week 24	14%	37%
ACR 70 (% responders)		
Week 14	4%	14%
Week 24	5%	20%

*p≤0.001 for all comparisons with the exception of ACR 70 response at Week 14 where p=0.008
[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.
An ACR 20 response (*Felson et al.*, 1995) was defined as:

1. ≥20% improvement in swollen joint count (66 joints) and tender joint count (68 joints); and
2. ≥20 % improvement in 3 of the following 5 assessments:

- Patient's assessment of pain on a 0–10 cm VAS scale (no pain to the worst possible pain)
- Patient's global assessment of disease activity on a 0–10 cm VAS scale (very well to very poor)
- Physician's global assessment of disease activity on a 0–10 cm VAS scale (no active arthritis to extremely active arthritis)
- Patient's assessment of physical function as measured by the HAQ on a scale of 0 to 3 (without any difficulty to unable to do)
- CRP

An ACR 50 or ACR 70 response was defined as ≥50% or ≥70% improvement in 1 and 2 above.

Among 89 patients randomized to SIMPONI® 50 mg + MTX, 70 patients were still on SIMPONI® 50 mg + MTX treatment at week 52. Among those, 64 (91%) and 43 (61%) out of 70 patients achieved DAS28 response and DAS28 remission, respectively. Forty-eight patients were still on SIMPONI® 50 mg + MTX treatment at week 104. Among those, 40 (83%), 33 (69%) and 24 (50%) out of 48 patients achieved ACR 20, 50 and 70 responses, respectively.

During the long term extension study, of those patients initially randomized to receive SIMPONI® 50 mg, 29 patients received only SIMPONI® 50 mg + MTX treatment through week 252. Among those, 26 (89.7%) showed an ACR 20 response at the last efficacy assessment (Week 256).

SIMPONI® 50 mg + MTX treatment also resulted in significantly greater improvement for each ACR component compared with treatment with placebo + MTX (Table 7).

TABLE 7: RA Study 1: Percent improvement in ACR components at Week 14 and 24; randomized patients		
	Placebo + MTX (N= 133)[a]	**SIMPONI® 50 mg + MTX* (N = 89)[a]**
Number of swollen joints		
Baseline (median)	12.0	13.0
Week 14	38%	62%
Week 24	32%	72%
Number of tender joints		
Baseline (median)	21.0	26.0
Week 14	30%	60%
Week 24	21%	62%
Patient's assessment of pain		
Baseline (median)	5.7	6.1
Week 14	18%	55%
Week 24	15%	50%
Patient's global assessment of disease activity		
Baseline (median)	5.3	6.0
Week 14	15%	45%
Week 24	17%	48%
Physician's global assessment of disease activity		
Baseline (median)	5.7	6.1
Week 14	35%	55%
Week 24	39%	62%
HAQ score		
Baseline (median)	1.25	1.38
Week 14	10%	29%
Week 24	7%	31%
CRP (mg/dl)		
Baseline (median)	0.8	1.0
Week 14	2%	44%
Week 24	0%	39%

*p≤0.001 for all comparisons.
[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.
Number of swollen joints: the number of swollen joints (0–66) were counted.
Number of tender joints: the number of tender joints (0–68) were counted.
Patient's assessment of pain: patients were asked to assess their average pain during the previous week on a VAS. The scale ranged from 0 (no pain) to 10 (worst possible pain) cm.
Patient's global assessment of disease activity: patients evaluated disease activity on a VAS global assessment of disease activity. The scale ranged from 0 (very well) to 10 (very poor) cm.
Physician's global assessment of disease activity: physicians evaluated disease activity on a VAS global assessment of disease activity. The scale ranged from 0 (no arthritis activity) to 10 (extremely active arthritis) cm.
HAQ: Disability Index of the Health Assessment Questionnaire assesses the degree of difficulty in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Improvement in HAQ scores (range 0–3) were calculated so that the positive values indicate improvement (i.e., less disability) and negative values indicate worsening.
CRP: (Normal Range 0.0–0.60 mg/dl)

RA Study 2 (GO-AFTER)
Treatment with SIMPONI® 50 mg in patients with active RA, previously treated with anti-TNF agent(s), resulted in significant improvement in signs and symptoms as demonstrated by ACR 20, 50 and 70 responses at Week 14 and 24 (Table 8).

When ACR 20 responses over time were considered, improvement was observed at the first assessment (Week 4) after the first SIMPONI® 50 mg + DMARDs (MTX, SSZ and/or HCQ) administration, and was maintained through Week 24.

TABLE 8: RA Study 2: Percent of RA patients with ACR responses at Week 14 and Week 24

	Placebo ± DMARDs[a] (N=150)[b]	SIMPONI® 50 mg ± DMARDs[a] (N=147)[b]	p-value
ACR 20 (% responders)			
Week 14	18%	35%	0.001
Week 24	16%	31%	0.002
ACR 50 (% responders)			
Week 14	7%	15%	0.021
Week 24	4%	16%	<0.001
ACR 70 (% responders)			
Week 14	2%	10%	0.005
Week 24	2%	9%	0.009

[a]DMARDs in Study RA-2 included MTX, HCQ, and/or SSZ (about 68%, 8%, and 5% of patients received MTX, HCQ, and SSZ, respectively).
[b]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.

During the long term extension study, of those patients initially randomized to receive SIMPONI® 50 mg, 21 patients had received only SIMPONI® 50 mg treatment through week 252. Among those, 12 (57.1%) had an ACR 20 response at the last efficacy assessment (Week 256).

Table 9 shows the percent of patients achieving an ACR 20 response by reported reason for discontinuation of one or more prior anti-TNF therapies.

TABLE 9: RA Study 2: Percent of ACR 20 responders by patient reported reason for discontinuation of one or more prior anti-TNF therapies[a]		
	Placebo ± DMARDs[b]	**SIMPONI® 50 mg ± DMARDs[b]**
ACR 20 Responders		
Lack of efficacy (% responders)		
n	94	82
Week 14	18%	35%*
Week 24	16%	29 %*
Intolerance (% responders)		
N	24	19
Week 14	17%	32%
Week 24	25%	37%
Other (% responders)		
N	62	58
Week 14	23%	38%
Week 24	21%	35%

[a]Patients previously treated with adalimumab, etanercept, or infliximab. Patients were required to provide a reason for discontinuation of each prior anti-TNF therapy that they had received.
[b]DMARDs in Study RA-2 included MTX, HCQ, and/or SSZ (about 68%, 8%, and 5% of patients received MTX, HCQ, and SSZ, respectively).
*p<0.05

SIMPONI® 50 mg treatment also resulted in significantly greater improvement for each ACR component compared with treatment with placebo. Swollen joint count for the SIMPONI® 50 mg and placebo group improved by 44% and 20%, respectively at Week 14 and 33% and 1%, respectively at Week 24. Improvement in tender joint count was 34% compared with 6% at Week 14, and 29% compared with -7% at Week 24, for the SIMPONI® 50 mg and placebo groups, respectively. Patients' and physicians' assessments and HAQ score were also significantly improved for SIMPONI® 50 mg compared with placebo at Week 14 and 24. For SIMPONI® 50 mg, there was a 37% improvement in CRP compared with 0% improvement for placebo at Week 14, and 15% compared with 0% at Week 24.

The percent of patients achieving a DAS 28 (using CRP) response was significantly greater for those patients treated with SIMPONI® 50 mg compared with those who received placebo at Week 14 (56% compared with 27%; p<0.001) and at Week 24 (45% compared with 21%; p<0.001).

RA Study 3 (GO-BEFORE)
This study evaluated patients with active RA who were MTX naïve and had not previously been treated with an anti-TNF agent. The co-primary endpoint was the percent of patients achieving an ACR 50 response at Week 24. The percent of randomized patients achieving an ACR 50 response with SIMPONI® + MTX compared to MTX plus placebo was not statistically significant (38.4 vs. 29.4%, p=0.053). The percentage of patients achieving an ACR 20 response at Week 24 (major secondary endpoint) was 62% for the SIMPONI® 50 mg + MTX group compared with 49% for the placebo + MTX group.

At Week 52, 60% and 42% of patients who received SIMPONI® 50 mg + MTX achieved ACR 20 and 50 responses, respectively, compared to 52% and 36% of patients who received MTX alone.

At Week 52, 15% of patients in the SIMPONI® 50 mg + MTX group achieved a major clinical response, defined as maintenance of an ACR 70 response over a continuous 6-month period, compared with 7% of patients in the placebo + MTX group.

During the long term extension study, of those patients initially randomized to receive SIMPONI® 50 mg, 62 patients had received only SIMPONI® 50 mg + MTX treatment through week 252. Among those, 45(72.6%) had an ACR 50 response at the last efficacy assessment (Week 256).

Radiographic Response
RA Study 3 (GO-BEFORE)
In study GO-BEFORE**,** the change from baseline in the vdH-S score (a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet) was used to assess the degree of structural damage. Key radiographic results for the SIMPONI® 50 mg dose group at Week 52 are presented in Table 10.

TABLE 10: Radiographic changes from baseline at Week 52 in Study GO-BEFORE

Changes From Baseline	Placebo + MTX n=160	SIMPONI® 50 mg +MTX n=159	Median Difference (95% CI)[a]	P-value*
Total vdH-S Score				
Mean ± SD	1.4 ± 4.6	0.7 ± 5.2		
Median (range)	0 (-9.0, 35.0)	0 (-12.4, 56.9)	0 (0.0, 0.5)	0.015
Erosion Score				
Mean ± SD	0.8 ± 2.8	0.4 ± 3.0		
Median (range)	0 (-5.5, 23.0)	0 (-12.4, 31.9)		
JSN Score				
Mean ± SD	0.6 ± 2.7	0.3 ± 2.5		
Median (range)	0 (-3.5, 25.9)	0 (-2.5, 25.0)		

*P-value from the van der Waerden test.
[a]Median difference and its 95% CI are estimated with Hodges-Lehman method.

At Week 52, 74% of patients in the SIMPONI® 50 mg + MTX group had no progression of structural damage as defined by a change from baseline in total vdH-S Score ≤ 0, compared to 58% in those with MTX plus placebo.

Improvement in Physical Function and Health-Related Quality of Life

RA Study 1 (GO-FORWARD)
Patients treated with SIMPONI® 50 mg showed significantly greater (p<0.001) improvement in the Disability Index of the Health Assessment Questionnaire (HAQ) score compared with placebo at Week 14 (mean ± SD 0.42 ± 0.50 vs. 0.16 ± 0.49) and Week 24 (mean ± SD 0.47 ± 0.55 vs. 0.13 ± 0.58). Among 89 subjects randomized to SIMPONI® 50 mg + MTX, 48 were still on this treatment at Week 104. The mean (± SD) improvement in HAQ score from baseline was 0.67 ± 0.64 in patients receiving SIMPONI® 50 mg + MTX. At Week 24, 47 (53.4%) patients treated with SIMPONI® 50 mg + MTX had an improvement in HAQ of ≥ 0.3 units, compared to 43 (33.9%) of patients treated with placebo + MTX. At Week 104, 40 out of 47 (85%) SIMPONI® 50 mg + MTX-treated patients maintained ≥ 0.3 units improvement in HAQ.

Patients treated with SIMPONI® 50 mg showed significantly greater improvement (p<0.001) from baseline in SF-36 physical component summary (PCS) score compared to placebo at Week 14 (mean change ± SD 8.0 ± 7.2 vs. 2.4 ± 7.8, respectively) and at Week 24 (mean change ± SD 8.3 ± 8.3 vs. 2.5 ± 8.1). At Week 104, the mean (± SD) improvement in SF-36 PCS score from baseline was 11.0 ± 9.7 in patients treated with SIMPONI® 50 mg + MTX (n=48).

Patients treated with SIMPONI® 50 mg showed significantly greater improvement (p<0.001) from baseline in the FACIT-F scores compared to placebo at Week 14 (mean ± SD 7.58 ± 8.93 vs. 2.27 ± 9.24) and at Week 24 (mean ± SD 7.30 ± 8.65 vs. 2.16 ± 9.53).

RA Study 2 (GO-AFTER)
The mean change from baseline in HAQ score at Week 24 was 0.23 ± 0.50 for the SIMPONI® 50 mg group compared with 0.03 ± 0.50 for the placebo group (p<0.001).

The mean (± SD) change from baseline for the FACIT-F score at Week 14 was 6.02 ± 10.14 for the SIMPONI® 50 mg group compared with 2.16 ± 9.74 for the placebo group (p=0.001).

Psoriatic Arthritis

Study Demographics and Trial Design
The safety and efficacy of SIMPONI® were evaluated in a single PsA study (GO-REVEAL), a multicentre, randomized, double-blind, placebo-controlled (through Week 24) study assessing treatment with SIMPONI® 50 mg or 100 mg administered as subcutaneous (SC) injections every 4 weeks in 405 adult patients with active PsA (Table 11). All patients randomized to placebo received SIMPONI® 50 mg after Week 24, but the trial remained double-blind until all patients had completed 52 weeks of treatment. At Week 52, patients entered the long-term extension phase. Patients receiving SIMPONI® 50 mg could have their dose increased to 100 mg at the discretion of the investigator. In addition, concomitant therapy with DMARDs (including MTX), corticosteroids, and NSAIDs could be added at the discretion of the investigator. Patients

enrolled in this study were men and women with a diagnosis of PsA for at least 6 months with a psoriatic skin lesion of at least 2 cm in diameter and active disease with at least 3 swollen and 3 tender joints despite disease-modifying antirheumatic (DMARD) or nonsteroidal anti-inflammatory (NSAID) therapy. Patients with each subtype of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%).

Patients were randomly assigned to placebo (n=113), SIMPONI® 50 mg (n=146), and SIMPONI® 100 mg (n=146). The co-primary endpoints were percent of patients achieving ACR 20 response at Week 14 and change from baseline in total PsA modified vdH-S score at Week 24. Major secondary endpoints included percent of patients achieving ACR 20 response at Week 24, Psoriasis Area Severity Index (PASI) 75 response at Week 14 in a subset of patients with ≥3% Body Surface Area (BSA) psoriasis skin involvement at baseline, improvement from baseline in HAQ scores at Week 24, and change from baseline in the PCS score of the SF-36 at Week 14. Through Week 252, the time point for the last scheduled study agent administration, 126 (31.1%) randomized subjects discontinued study agent. Efficacy data were collected and analyzed through Week 256. Through Week 252, the time point for the last scheduled study agent administration, 43 (29.4%) treated subjects initially randomized to receive golimumab 50 mg, continually received the authorized dose of golimumab 50 mg once a month.

TABLE 11: Summary of controlled clinical trials supporting safety and efficacy in patients with PsA

Study	Trial Design	Dosage: Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
PsA (GO-REVEAL)	Multicentre, double-blind, randomized, placebo-controlled	SIMPONI® 50 mg; sc; q4w for 104 weeks	146	45.7 ± 10.70 (23, 78)	39.0%
		SIMPONI® 100 mg; sc; q4w for 104 weeks	146	48.2 ± 10.93 (20, 77)	41.1%
		Placebo	113	47.0 ± 10.56 (24, 70)	38.9%

Study results

Reduction in Signs and Symptoms

No clinically meaningful differences across efficacy measures were apparent between the SIMPONI® 50 mg and 100 mg dosing regimens in the Phase 3 PsA study. By study design, patients in the long-term extension may have their dose modified at the discretion of the study physician.

Treatment with SIMPONI® 50 mg resulted in significant improvement in signs and symptoms as demonstrated by percent of patients achieving ACR 20 response at Week 14 ($p<0.001$). Responses observed in the SIMPONI®-treated groups were similar in patients receiving and not receiving concomitant MTX (Table 12).

TABLE 12: PsA Study: ACR 20 response at Week 14 stratified by baseline MTX use; randomized patients

	Placebo	SIMPONI® 50 mg
Subjects randomized	113	146
ACR 20		
N	113	146
Subjects in response	10 (8.8%)	74 (50.7%)
p-value		<0.001
Subjects receiving MTX at baseline		
N	55	71
Subjects in response	8 (14.5%)	38 (53.5%)
Subjects not receiving MTX at baseline		
N	58	75
Subjects in response	2 (3.4%)	36 (48.0%)

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ACR 20 improvement was observed at the first assessment (Week 4) after the first SIMPONI® administration, and was maintained through Week 24 (Figure 2).

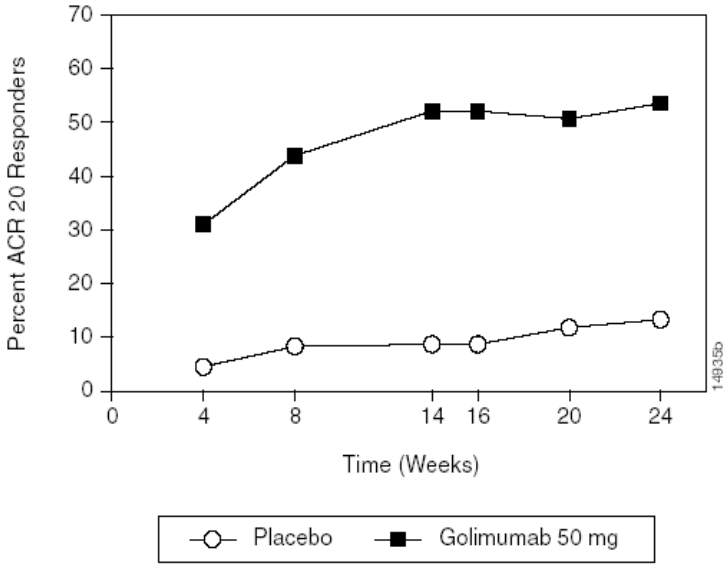


Figure 2: Percent of ACR 20 responders through Week 24; randomized patients in placebo and SIMPONI® 50 mg dose groups

The percent of patients achieving an ACR 50 response at Week 14 was 30% and 2%, and at Week 24 was 32% and 4% for the SIMPONI® 50 mg and placebo groups, respectively

(p<0.001). The percent of patients achieving an ACR 70 response was 12% and 1% at Week 14, and at Week 24 was 19% and 1% for the SIMPONI® 50 mg and placebo groups, respectively (p<0.001). Of the 146 subjects randomized to SIMPONI® 50 mg, 70 patients remained on this dose at Week 104. Of these 70 patients, 64 (91.4%), 46 (65.7%) and 31 (44.3%) patients achieved ACR 20, 50 and 70 responses, respectively. Of the 146 subjects randomized to SIMPONI® 50 mg, 43 patients remained on the SIMPONI® 50 mg dose through Week 252. Of these, 37 (86%) patients had an ACR 20 response at the last efficacy assessment (Week 256).

Responses observed in the SIMPONI® 50 mg group were similar in patients receiving and not receiving concomitant MTX.

The percent of patients achieving Psoriatic Arthritis Response Criteria (PsARC) and DAS 28 response (using CRP) was also significantly greater in the SIMPONI® 50 mg group compared with placebo at Week 14 and 24 (p<0.001).

SIMPONI® treatment also resulted in significantly greater improvement compared with placebo for each ACR component (p<0.001, Table 13).

TABLE 13: PsA Study: Percent improvement in ACR components at Weeks 14 and 24; randomized patients

	Placebo (N=113)[a]	**SIMPONI® 50 mg* (N=146)[a]**
Number of swollen joints		
Baseline (median)	10.0	11.0
Week 14	8%	60%
Week 24	0%	67%
Number of tender joints		
Baseline (median)	18.0	19.0
Week 14	0%	54%
Week 24	-6%	66%
Patient's assessment of pain		
Baseline (median)	5.4	5.8
Week 14	-1%	48%
Week 24	-2%	50%
Patient's global assessment of disease activity		
Baseline (median)	5.2	5.2
Week 14	2%	49%
Week 24	-2%	52%
Physician's global assessment of disease activity		
Baseline (median)	5.2	5.4
Week 14	7%	59%
Week 24	5%	71%
HAQ score		
Baseline (median)	1.0	1.0
Week 14	0%	28%

TABLE 13: PsA Study: Percent improvement in ACR components at Weeks 14 and 24; randomized patients		
	Placebo (N=113)[a]	**SIMPONI® 50 mg* (N=146)[a]**
Week 24	0%	33%
CRP (mg/dL)		
Baseline (median)	0.60	0.60
Week 14	0%	40%
Week 24	0%	29%

*p-values < 0.001 for all comparisons.
[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.
CRP: Normal Range: 0.0–0.60 mg/dl

At Week 14 in patients with enthesitis at baseline, there was a significantly greater improvement from baseline in enthesitis score as measured by PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) with SIMPONI® 50 mg compared with placebo (median 50% vs. 0%; p<0.001). Significant improvement was maintained through Week 24.

In patients with dactylitis at baseline, the improvement in dactylitis score was numerically greater in the SIMPONI® 50 mg treatment group than in the placebo treatment group at both Week 14 and at Week 24 (median 76% vs. 0%, p=0.10; 100% vs. 42%, p=0.09 respectively).

Psoriasis Skin and Nail Response

Among patients with ≥3% BSA psoriasis skin involvement at baseline, a significantly greater percent of patients achieved PASI 75 response at Week 14 when treated with SIMPONI® 50 mg compared with placebo. The percent of patients achieving a PASI 50 and 90 response in the SIMPONI® 50 mg group at Week 14 was also greater than in placebo group (Table 14). The responses were maintained or increased through Week 24. Of the 109 subjects randomized to golimumab 50 mg and with ≥ 3% BSA psoriasis skin involvement at baseline, 48 patients were still on this treatment at Week 104. Of 48 patients, 33 (68.8%) achieved PASI 75 response at week 104.

TABLE 14: PsA Study: PASI response at Week 14; randomized patients with ≥3% BSA involvement at baseline		
	Placebo (N=113)[a]	**SIMPONI® 50 mg* (N=146)[a]**
Patients with ≥3% BSA involvement at baseline	**79**	**109**
PASI 50 (% responders)	10 %	59 %
PASI 75 (% responders)	3 %	40 %
PASI 90 (% responders)	0 %	21 %

*p-values < 0.001 for PASI 50, 75, and 90.
[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.

PASI is an index used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that ranges from 0 to 72.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20% and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration, and scaling, which are each rated on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe).

Each region is also assessed for the area of involvement for psoriatic lesions on a scale of 0 to 6 with 0 as no involvement and 6 as 90%–100% involvement.

Nail physician global assessment (PGA) and Nail Psoriasis Severity Index (NAPSI) analyses were performed on patients with fingernail involvement at baseline. Percent change from baseline in NAPSI and improvement in nail PGA were significantly greater in patients treated with SIMPONI® 50 mg as compared with placebo at both Week 14 and at Week 24 ($p \leq 0.015$).

Radiographic Response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified for PsA by addition of hand distal interphalangeal (DIP) joints. Key radiographic results for the SIMPONI® 50 mg dose at Week 24 are presented in Table 15.

Table 15: PsA Study: Radiographic changes from baseline at Week 24

Changes from Baseline	Placebo n=113	SIMPONI® 50 mg n=146	Median Difference (95% CI)[a]	P-value*
Total vdH-S Score				
Mean ± SD	0.27 ± 1.26	-0.16 ± 1.31		
Median (range)	0 (-4.5, 6.5)	0 (-7.1, 5.0)	0 (0.0, 0.5)	0.011
Erosion Score				
Mean ± SD	0.29 ± 0.91	-0.12 ± 0.99		
Median (range)	0 (-2.5, 3.5)	0 (-5.7, 2.0)		
JSN Score				
Mean ± SD	-0.03 ± 0.65	-0.04 ± 0.57		
Median (range)	0 (-3.0, 4.5)	0 (-2.0, 3.0)		

*: P value from the van der Waerden test.
a: Median difference and its 95% CI are estimated with the Hodges-Lehman method.

The number of patients in the individual PsA subtypes was too small to derive meaningful conclusions on the effect of SIMPONI® in each of the PsA subtypes.

At Week 24, 81% (118/146) of patients in the SIMPONI® 50 mg group had no progression of structural damage (as defined by a change from baseline in total vdH-S Score ≤0) compared to 66% in those receiving placebo. Of the 146 patients initially randomized to SIMPONI® 50 mg, X-ray data were available for 101 and 66 patients who remained on this treatment at Weeks 52 and 104, respectively. Of these patients, 77% (78/101) and 76% (50/66) of patients showed no progression from baseline at week 52 and week 104, respectively.

Improvement in Physical Function and Health-Related Quality of Life
In the PsA Study, patients treated with SIMPONI® 50 mg showed significantly greater ($p<0.001$) improvement in the HAQ score compared with placebo at Week 14 (mean ± SD 0.31 ± 0.50 vs. 0.04 ± 0.44;) and Week 24 (mean ± SD 0.33 ± 0.55 vs. -0.01 ± 0.49).

At Week 24, the percent of patients who achieved clinically meaningful improvements in HAQ of ≥0.30 change from baseline was also significantly greater in those patients receiving SIMPONI® 50 mg when compared with placebo ($p<0.001$). At Week 104, 69 of the 146 (47.3%) patients randomized to SIMPONI® 50 mg were still on this dose. The mean (± SD) improvement in HAQ score from baseline in these 69 patients was 0.54 ± 0.55.

In the PsA study, patients treated with SIMPONI® 50 mg showed significantly greater improvement ($p<0.001$) from baseline in the SF-36 physical component summary (PCS) score compared to placebo at Week 14 (mean change ± SD 6.5 ± 8.9 vs. 0.6 ± 7.7) and at Week 24 (mean change ± SD 7.4 ± 9.2 vs. 0.7 ± 8.7).

Patients treated with SIMPONI® 50 mg showed significantly greater improvement from baseline ($p<0.05$) in SF-36 mental component summary (MCS) score compared to placebo at Week 14 (mean ± SD 2.8 ± 10.3 vs. 0.4 ± 11.4) and Week 24 (mean ± SD 3.4 ± 10.5 vs. -0.6 ± 12.1).

Ankylosing Spondylitis

Study Demographics and Trial Design

The safety and efficacy of SIMPONI® were evaluated in an AS Study (GO-RAISE), a multicentre, randomized, double-blind, placebo-controlled (through Week 24) study assessing treatment with SIMPONI® 50 mg or 100 mg administered as subcutaneous (SC) injections every 4 weeks in 356 adult patients with active AS (Table 16). Patients enrolled in this study were men and women who had symptoms of active disease (defined as a BASDAI ≥4 and a VAS for total back pain of ≥4, each on a scale of 0 to 10 cm) despite current or previous disease modifying antirheumatic drug (DMARD) or nonsteroidal anti-inflammatory drug (NSAID) therapy. Patients with complete ankylosis of the cervical and lumbar spine were excluded from study participation. Through Week 252, the time point for the last scheduled study agent administration, 101 (28.5%) randomized subjects discontinued study agent. Efficacy data were collected and analyzed through Week 256. Through Week 252, the time point for the last scheduled study agent administration, 68 (49.3%) treated subjects initially randomized to receive golimumab 50mg, continually received the authorized dose of golimumab 50 mg once a month

Patients were randomly assigned to placebo (n=78), SIMPONI® 50 mg (n=138) and SIMPONI® 100 mg (n=140). Placebo-controlled efficacy data were collected and analyzed through Week 24. The primary endpoint was Assessment in Ankylosing Spondylitis 20 (ASAS 20) response at Week 14. Major secondary endpoints included ASAS 20 response at Week 24, Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14, and Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14.

TABLE 16: AS Study: Summary of controlled clinical trials supporting safety and efficacy in patients with AS

Study	Trial Design	Dosage: Route of Administration and Duration[a]	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
AS (GO-RAISE)	Multicentre, double-blind, randomized, placebo-controlled	SIMPONI® 50 mg or 100 mg; sc; q4w for up to 24 weeks SIMPONI® Placebo	278 78	39.3 ± 12.06 (18, 83)	28.4%

[a]Duration of controlled period

Study results

Reduction in signs and symptoms

In general, no clinically meaningful differences across efficacy measures were apparent between the SIMPONI® 50 mg and 100 mg dosing regimens in the Phase 3 AS study. During the long term extension patients may have their dose modified at the discretion of the study physician.

At Week 14, ASAS 20/40 responses were achieved by 59% and 45% respectively, of patients receiving SIMPONI® 50 mg compared with 22% and 15% respectively of patients receiving placebo ($p<0.001$, Table 17). Improvement in signs and symptoms as measured by ASAS 20 was observed at the first assessment (Week 4) after the first SIMPONI® administration, and was maintained through week 24 (Figure 3).

Among 68 patients who remained on the SIMPONI® 50 mg dose through Week 252, 59(86.8%) patients had an ASAS 20 response at the last efficacy assessment (Week 256).

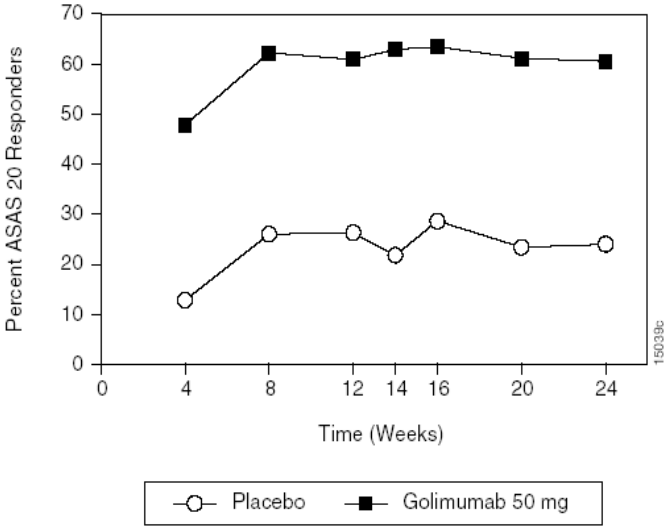


Figure 3: Percent of AS patients achieving ASAS 20 response through Week 24; randomized patients in placebo and SIMPONI® 50 mg dose groups

TABLE 17: AS Study: Percent of AS patients with ASAS responses; randomized patients

	Placebo (N=78)[a]	**SIMPONI® 50 mg* (N=138)[a]**
ASAS 20 (% responders)		
Week 14	22%	59%
Week 24	23%	56%
ASAS 40 (% responders)		
Week 14	15%	45%
Week 24	15%	44%

* $p \leq 0.001$ for all comparisons.

[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint

An ASAS 20 response (*Anderson et al.*, 2001) was defined as: (1). An improvement of ≥20% from baseline and an absolute improvement from baseline of at least 1 on a 0 to 10 cm scale in at least 3 of the following 4 domains: Patient global assessment, Pain (total back pain) assessment, BASFI score, or Inflammation (average of the first 2 questions of the BASDAI concerning morning stiffness) (2). Absence of deterioration from baseline (deterioration defined as ≥20% worsening and absolute worsening of at least 1 on a 0 to 10 cm scale) in the potential remaining domain.

ASAS 40: An ASAS 40 is defined as ≥40% improvement in 3 of 4 domains, with an absolute improvement of at least 2 on a 0 to 10 cm scale, and no deterioration in the remaining domain.

Patients treated with SIMPONI® 50 mg achieved significantly greater improvements in all ASAS 20 components compared with placebo (Table 18).

TABLE 18: AS Study: Improvement in ASAS components; randomized patients		
	Placebo (N=78)[a]	**SIMPONI® 50 mg* (N=138)[a]**
Patient's global assessment of disease activity[b]: (median change from baseline)		
Baseline (median)	7.2	7.0
Week 14	-0.8	-2.8
Week 24	-0.2	-2.6
Total back pain[b]: (median change from baseline)		
Baseline (median)	7.6	7.5
Week 14	-0.8	-3.5
Week 24	-0.4	-3.5
Inflammation[c]: (median change from baseline in morning stiffness)		
Baseline (median)	7.1	7.1
Week 14	-0.5	-3.2
Week 24	-0.2	-3.6
Night back pain[b]: (median change from baseline)		
Baseline (median)	7.4	7.1
Week 14	-0.3	-3.0
Week 24	-0.4	-3.1
C-reactive protein[d]: (median change from baseline in mg/dL)		
Baseline (median)	1.2	1.1
Week 14	0	-0.7
Week 24	0	-0.7

*p<0.001 for all comparisons
[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint.
[b]Visual Analogue Scale (with 0 = "best" and 10 = "worst"). A negative/decreasing score is indicative of improvement.
[c]Average of last 2 questions on the 6-question BASDAI.
[d]Normal range 0-0.6 mg/dL

Additional measures of efficacy such as ASAS partial remission, ASAS 5/6 response, and BASDAI 50, 70, and 90 were statistically significant at Weeks 14 and 24 for SIMPONI® 50 mg compared with placebo (p<0.001).

Improvement in Physical Function

Median improvement in the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14 was 1.4 in the SIMPONI® 50 mg group, compared with worsening by 0.1 in the placebo group (p <0.001). The improvement in physical function was maintained at week 24 in SIMPONI®-treated patients.

Improvement in Range of Motion

No significant change in BASMI was observed at Weeks 14 or 24 in the SIMPONI® 50 mg

group compared with the placebo group. However, in the 50 mg SIMPONI® group vs. placebo, significant median improvements from baseline were observed at Weeks 14 and 24 for lumbar flexion, lumbar side flexion at Week 24, and intermalleolar distance measurements at both Weeks 14 and Week 24 ($p<0.05$).

Improvement in Health-Related Quality of Life

In the AS study, patients treated with SIMPONI® 50 mg showed significantly greater improvement from baseline ($p<0.001$) in SF-36 physical component summary (PCS) score compared to placebo at Week 14 (mean change ± SD 8.8 ± 9.6 vs. 3.0 ± 7.2) and was maintained through Week 24.

Improvement in Sleep

Patients treated with SIMPONI® 50 mg showed significantly greater median improvement from baseline in sleep scores, as measured by the 20-point Jenkins Sleep Evaluation Questionnaire, compared with placebo at Week 14 (-3.0 vs. 0.0; $p<0.001$) and Week 24 (-3.0 vs. -1.0; $p<0.001$).

Non-radiographic Axial Spondyloarthritis

Study demographics and trial design

The safety and efficacy of SIMPONI® 50 mg administered subcutaneously every 4 weeks were evaluated in a multi-center, randomized, double-blind, placebo-controlled (through Week 16) study (GO-AHEAD) in adult patients with severe active nr-Ax SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but that did not meet the modified New York criteria for AS). Subjects had a diagnosis of active Axial SpA of ≤5 years duration, and chronic back pain of ≥ 3 month duration. All eligible subjects were to be randomized in a 1:1 ratio to either the golimumab 50 mg treatment arm (N = 98) or the placebo treatment arm (N = 100). Subjects were stratified based on CRP level (limited to ≤60% of patients with CRP levels below the upper limit of normal at baseline) and evidence of sacroiliitis (active inflammation) on MRI (limited to ≤50% of patients with no MRI evidence of sacroiliitis at baseline). Subjects who successfully completed Part 1 (Weeks 0-16), were eligible to participate in Part 2 (Weeks 16-48) of the trial in which all patients received SIMPONI® 50 mg administered subcutaneously every 4 weeks through Week 48. Efficacy assessments were performed through Week 52 and safety follow-up through Week 60. Approximately 93% (176/189) of patients who were receiving SIMPONI® at the beginning of the open-label extension (Week 16) remained on treatment through the end of the study (Week 52).
Patients enrolled in this study had active disease, defined as a BASDAI ≥ 4 cm and a VAS for total back pain of ≥ 4 cm, each on a scale of 0 to 10 cm, and either experienced an inadequate response to NSAID therapy or were intolerant to NSAID therapy.

Patients who previously received TNF-α blockers or any biological agents were excluded from the study.

The primary endpoint was ASAS 20 response at Week 16. Major secondary endpoints included ASAS 40 response at Week 16, BASDAI 50 response at Week 16, ASAS partial remission at Week 16, and the change in the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI sacroiliac joints score from baseline to Week 16.

Baseline demographics and disease characteristics were generally comparable across both treatment groups. At baseline, the majority of patients (67%) had a diagnosis of nr-Ax SpA of less than 1 year duration. The mean BASDAI score at baseline was 6.5±1.5 cm. Approximately 81% of the total patient population at baseline received concomitant NSAID therapy. Approximately 41% of patients showed elevated CRP levels > upper limit of normal, 67% of subjects had evidence of sacroiliitis on MRI, and 80% showed evidence of elevated CRP levels >upper limit of normal and/or evidence of sacroiliitis on MRI. Most patients were male (57%), all (100%) were Caucasian, and the mean age was 31.2 (±7.2) years.

Analyses were performed on the All Treated population (AT, N=197). A subpopulation defined by elevated CRP above the upper limit of normal and/or evidence of sacroiliitis on MRI at baseline (n=158/197, 80.2%) was also evaluated.

Reduction in signs and symptoms

Treatment with SIMPONI® 50 mg resulted in improvement in signs and symptoms as demonstrated by the proportion of subjects with an ASAS 20 response at Week 16 (Table 19). Figure 4 shows the proportion of subjects achieving ASAS 20 responses by visit.

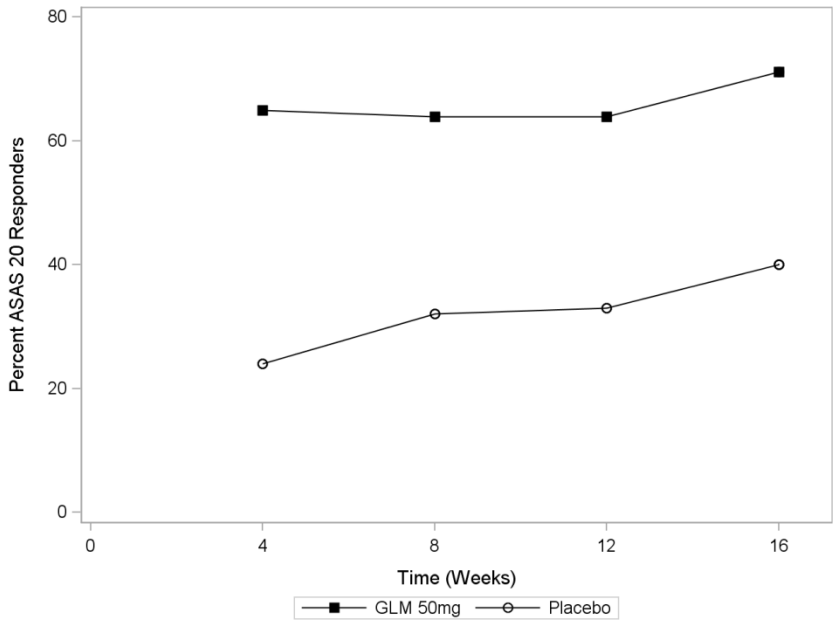


Figure 4*: Percent of Subjects Achieving ASAS 20 by Time Point All Treated (AT)

(*the same subject may not have responded at each timepoint)

Table 19: Percent of nr-Ax SpA patients with ASAS responses at Week 16 ; randomized and treated patients		
	All treated population (AT)	
	Placebo	SIMPONI® 50 mg
n[a]	100	97
Responders, % of patients		
ASAS 20	40%	71%
Difference in % vs placebo (95% CI)	31.2 (17.5, 43.6)	
p-value*	<0.0001**	
ASAS 40	23%	57%
Difference in % vs placebo (95% CI)	33.8 (20.4, 46.1)	
p-value*	<0.0001**	
Premature discontinuation from the placebo-controlled period (week 16) for any reason: golimumab 50 mg group, n=4 (2%); placebo group, n= 3 (1.5%). All patients who discontinued prior to week 16 were considered non-responder for analyses of response.		
Concomitant NSAID use: placebo 80/100, (80%); golimumab 50 mg 80/97 (82.5%)		

[a] n reflects randomized and treated patients

*Type I error was controlled using a closed testing procedure.

** Derived based on the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes or no) and screening CRP level (≤ upper limit of normal or > upper limit of normal) as stratification factors.

The proportion of subjects achieving BASDAI 50 response at Week 16 in the golimumab 50 mg group (57.7%) was significantly greater (p<0.0001) than in the placebo group (30.0%).

The proportion of subjects achieving ASAS partial remission at Week 16 in the golimumab 50 mg group (33.0%) was significantly greater (p=0.0136) than in the placebo group (18.0%).

In the subpopulation of patients with elevated CRP (> the upper limit of normal) and/or evidence of sacroiliitis on MRI at baseline, comparable results to the AT population were observed in ASAS 20, ASAS 40, BASDAI 50 and ASAS partial remission.

Among subjects treated with golimumab 50 mg who remained on treatment through the end of the study (Week 52), improvements in ASAS 20, ASAS 40, BASDAI 50, and ASAS partial remission were comparable to those reported at Week 16.

Table 20 shows the percent improvement in the components of the ASAS response criteria for the SIMPONI® 50 mg and placebo groups at Week 16.

Table 20: Improvements in ASAS 20 Components at Week 16: All Treated Population (AT) (Mean (SD))

	SIMPONI® 50 mg (n=97)			Placebo (n=100)		
ASAS 20 Response Components	Baseline	Week 16	Change from baseline at week 16	Baseline	Week 16	Change from baseline at week 16
Patient global assessment (0-10)	6.96 (1.94)	2.98 (2.91)	-3.70 (0.32)	6.23 (2.22)	4.97 (3.18)	-1.49 (0.31)
Total Back Pain (0-10)	6.98 (1.78)	2.77 (2.78)	-4.09 (0.30)	6.61 (1.67)	4.74 (3.17)	-1.96 (0.29)
BASFI (0-10)[a]	5.26 (2.38)	2.50 (2.53)	-2.63 (0.23)	4.70 (2.53)	3.87 (2.83)	-0.91 (0.22)
Inflammation (0-10)[b]	6.80 (1.89)	2.84 (2.48)	-3.82 (0.25)	6.10 (2.05)	4.39 (2.80)	-1.81 (0.24)

a BASFI is Bath Ankylosing Spondylitis Functional Index

b Inflammation is the mean of 2 patient-reported stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI).

Spinal mobility was assessed by BASMI. The mean change from baseline in BASMI score at Week 16 in the golimumab 50 mg-treated group was -0.5 cm vs. -0.1 cm in the placebo-treated group.

The mean change from baseline in CRP at week 16 was -0.99 mg/dL in the golimumab 50 mg group and was -0.35 mg/dL in the placebo group.

The mean change from baseline in the SPARCC (Spondyloarthritis Research Consortium of Canada) MRI SI joints score was -5.3 in the golimumab 50 mg group and was -0.9 in the placebo group at Week 16.

The change from baseline in the ASQoL score at Week 16 was -5.2 in the golimumab 50 mg group and -1.8 in the placebo group.

Ulcerative Colitis

Study demographics and trial design

The safety and efficacy of SIMPONI® were evaluated in two multi-center, randomized, double-blind, placebo-controlled Phase 3 clinical studies in patients ≥ 18 years of age.

TABLE 21: Summary of controlled clinical trials supporting safety and efficacy in patients with UC

Study #	Trial Design	Dosage: Route of Administration and Duration	Study Subjects[a] (n)	Median Age (Range)	Gender
UC Study 1 (PURSUIT - Induction)	Multicentre, double-blinded, randomized, placebo-controlled	SC administration at Week 0, and Week 2:		38 (29,50)	M:596 F:469
		placebo	331		
		SIMPONI® 100 mg→ 50 mg	72		
		SIMPONI® 200 mg→ 100 mg	331		
		400 mg→ 200 mg	331		
UC Study 2 (PURSUIT - Maintenance)	Multicentre, double-blinded, randomized, placebo-controlled	SC administration at Week 0, and then q4w through Week 52		39 (18-79)	M:241 F:223
		placebo	156		
		SIMPONI® 50 mg	154		
		SIMPONI® 100 mg	154		

[a] The safety evaluations for PURSUIT maintenance includes 464 randomized subjects as tabulated above, and 764 non randomized subjects

UC Study 1 (PURSUIT-Induction)

UC Study 1 was an induction study conducted in patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or had failed to tolerate conventional therapies, or were corticosteroid dependent. The study was a combination Phase 2 (dose finding) and Phase 3 (dose confirming) study. In the dose finding portion of the study, patients were randomized to one of 4 treatment groups: 400 mg SIMPONI® SC at Week 0 and 200 mg at Week 2 (400/200 mg), 200 mg SIMPONI® SC at Week 0 and 100 mg at Week 2 (200/100 mg), 100 mg SIMPONI® SC at Week 0 and 50 mg at Week 2 (100/50 mg), or placebo SC at Weeks 0 and 2. In the dose confirming portion of the study, efficacy was evaluated in 761 patients who were randomized to receive either 400 mg SIMPONI® SC at Week 0 and 200 mg at Week 2, 200 mg SIMPONI® SC at Week 0 and 100 mg at Week 2, or placebo SC at Weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted.

UC Study 2 (PURSUIT-Maintenance)

UC Study 2 was a maintenance study that evaluated 456 patients who achieved clinical response with SIMPONI® induction. Patients were randomized to receive SIMPONI® 50 mg, SIMPONI® 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates and/or immunomodulatory agents were permitted. Corticosteroids were to

be tapered at the start of the maintenance study. The efficacy of SIMPONI® through Week 54 was assessed in this study. Patients who completed the maintenance study through Week 54 continued treatment through Week 216. Efficacy assessments were performed through the extension study.

Clinical Endpoints

The primary endpoint for UC Study 1 (PURSUIT-Induction) was clinical response at Week 6. The major secondary endpoints were clinical remission, mucosal healing (improvement of endoscopic appearance of the mucosa), and the improvement in the IBDQ score, all at Week 6. The primary endpoint for UC Study 2 (PURSUIT-Maintenance) was maintenance of clinical response through Week 54. Selected major secondary endpoints included clinical remission at both Week 30 and Week 54 and mucosal healing at both Week 30 and Week 54.

In both studies, clinical response and clinical remission were defined based on the Mayo score, which consists of four subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician's global assessment. Each subscore is rated on a scale from 0 to 3, indicating normal (0) to severe (3) activity. The Mayo score is the sum of the 4 subscores. Clinical response was defined as a decrease from Week 0 of induction in the Mayo score of ≥ 30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. Clinical remission was defined as a Mayo score ≤ 2 points, with no individual subscore >1. Improvement of endoscopic appearance of the mucosa (study endpoint, mucosal healing) was defined as a Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

In UC Study 2, patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). A patient who maintained response was in a state of continuous clinical response at each evaluation through Week 54. Similarly, a patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through Week 54) to achieve durable remission.

Health-related quality of life was assessed using the IBDQ, SF-36 and the EQ-5D. The IBDQ is a questionnaire specifically designed for patients with inflammatory bowel disease. The SF-36 is a general health status questionnaire that has been widely used in various diseases and conditions to assess patients' physical and mental well being. The EQ-5D is a standardized non-disease specific instrument for describing and valuing health-related quality of life.

Approximately 63% (358/570) of patients, who were receiving SIMPONI® at the beginning of the study extension (Week 56), remained on treatment through the end of the study (last SIMPONI® administration at Week 212).

Study results

The results for clinical endpoints during induction treatment are based on patients randomized during the dose confirming part of UC Study 1(PURSUIT-Induction, n=504). The results for clinical endpoints during maintenance treatment are based on patients from UC Study 2

(PURSUIT-Maintenance) who achieved clinical response with SIMPONI® from previous induction with golimumab (n=456).

Clinical Response, Clinical Remission, and Improvement of Endoscopic Appearance of the Mucosa

In UC Study 1, a significantly greater percentage of patients in the SIMPONI® group achieved clinical response, clinical remission and endoscopic improvement of the mucosa when compared to placebo at Week 6.

The data from UC Study 2 demonstrate that the proportion of patients who maintained clinical response through Week 54 was significantly greater in the SIMPONI® 100 mg group compared with the placebo group. Additionally, the proportion of patients in clinical response who achieved clinical remission and improvement of endoscopic appearance of the mucosa at both Weeks 30 and 54 were significantly greater in the SIMPONI® 100 mg group compared with the placebo group.

TABLE 22: The Proportion of Patients with UC in Clinical Response, Clinical Remission and with Improvement of Endoscopic Appearance of the Mucosa in Studies UC-1 and UC-2

Study UC-1 (6-Week Induction Study)			
	Placebo N=251	**SIMPONI® 200/100 mg N=253**	**Treatment difference (95% C.I.)**
Clinical response[a] at Week 6	30%	51%	21% (12%, 29%)[*]
Clinical remission[a] at Week 6	6%	18%	11% (6%, 17%)[*]
Improvement of endoscopic appearance of the mucosa at Week 6[a]	29%	42%	14% (5%, 22%)[†]
Study UC-2 (54-Week Maintenance Study)[b]			
	Placebo N=154	**SIMPONI® 50 mg N=151**	**SIMPONI ®100 mg N=151**
Clinical response[a] through Week 54[c] *Treatment Difference* *95% CI*	31%	47% 16% (5%, 27%)[¶]	50% 19% (8%, 29%)[‡]
Clinical remission[a] at both Week 30 and Week 54[d] *Treatment difference* *95% CI*	16%	23% 8% (-1%, 16%)	28% 12% (3%, 21%)[§]

[*] p<0.0001; [†] p=0.0014; [‡] p<0.001; [§] p=0.004; [¶]p=0.01 [a] Patients who had a prohibited change in concomitant UC medication, an ostomy or colectomy, discontinued study agent due to lack of therapeutic effect, or a dose adjustment in Study UC-2 were considered not to be in clinical response, clinical remission or have an improvement in endoscopic appearance of the mucosa from the time of the event onward.

[b] Results in Study UC-2 are based on patients who were in clinical response to SIMPONI® at study entry.

[c] Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained clinical response was in response at each evaluation through Week 54.

[d] A patient had to be in remission at both weeks 30 and 54 (without demonstrating a loss of response at any time point through Week 54) to achieve sustained remission.

More SIMPONI®-treated patients demonstrated sustained improvement of endoscopic

appearance of the mucosa at both Week 30 and Week 54 in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Mayo Score

In UC Study 1 (PURSUIT-Induction), a greater reduction in the partial Mayo score was evident as early as Week 2 in the SIMPONI® 200/100 mg group compared with the placebo group and this reduction was maintained through Week 6.

The reduced median partial Mayo score (at Week 0 of UC Study 2) was maintained in the SIMPONI® 100 mg group through Week 52 and in the SIMPONI® 50 mg group through Week 48; the median partial Mayo score in the placebo group increased after Week 8 and continued to increase over time to a value at Week 54 approaching the value prior to golimumab induction.

The proportion of subjects in UC Study 2 that maintained improvement in each Mayo subscore from Week 0 through Week 54 in UC Study 2 was greater in 100 mg group compared to the placebo group.

Among patients who entered the study extension, the proportion of subjects with inactive or mild disease activity as assessed by the Physician's global assessment subscore of the Mayo score was generally sustained through Week 216.

Health-related Quality of Life

In UC Study 1 (PURSUIT-Induction), the mean improvement from baseline in IBDQ score at Week 6 was significantly greater in the SIMPONI® 200/100 mg group, 27.0 ± 33.72, compared with the placebo group, 14.8 ± 31.25; $p<0.0001$.

SIMPONI® I.V.

Rheumatoid Arthritis

Study demographics and trial design

The efficacy and safety of SIMPONI® I.V. were evaluated in a multicentre, randomized, double-blind, placebo-controlled trial, IV RA Study 1 (GO-FURTHER) in 592 patients ≥18 years of age with moderately to severely active RA despite concurrent methotrexate (MTX) therapy and who had not been previously treated with a biologic TNF-blocker. Patients were diagnosed according to American College of Rheumatology (ACR) criteria, at least 3 months prior to administration of study agent and were required to have at least 6 swollen and 6 tender joints. Patients were randomized to receive either SIMPONI® I.V. 2 mg/kg (n=395) or placebo (n=197) over a 30 minute intravenous infusion at Weeks 0, 4 and every 8 weeks thereafter in addition to their weekly maintenance MTX dose. All patients receiving placebo + MTX received SIMPONI® I.V. 2 mg/kg IV + MTX after Week 24, but the trial remained double-blind until all patients had completed 52 weeks of treatment. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs. All

patients were maintained on their stable dose of MTX (15-25 mg/week) throughout the study. The use of other DMARDs including cytotoxic agents or other biologics was prohibited. The primary endpoint was the percent of patients achieving ACR 20 response at Week 14. Major secondary endpoints included the proportion of subjects with a moderate or good DAS28 response (using CRP), change from baseline in HAQ-DI at Week 14, the proportion of subjects with an ACR 50 response, and the change from baseline in modified van der Heijde-Sharp (vdH-S) score at Week 24. Efficacy data were collected and analyzed through Week 52.

TABLE 23: Summary of Controlled Clinical Trial Supporting Efficacy in Patients with RA

Study #	Trial Design	Dosage: Route of Administration and Duration[a]	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
IV RA Study 1 (GO-FURTHER)	Multicentre, double-blind, randomized, placebo-controlled	SIMPONI® I.V. 2 mg/kg infusion at Week 0, 4, and every 8 weeks thereafter for 24 weeks	395	52 (18,83)	81.6%
		Placebo	197		

[a]Duration of controlled period

Study results

Clinical Response

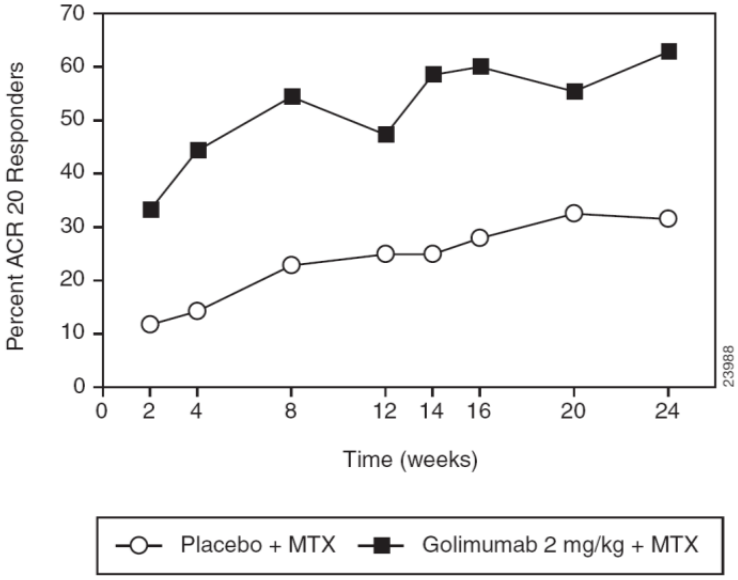
A greater percentage of patients treated with the combination of SIMPONI® I.V. + MTX achieved ACR 20 at Week 14 and ACR50 at Week 24 versus patients treated with the placebo + MTX as shown in Table 24. The percent of patients achieving ACR 20 responses by visit for RA IV Study 1 is shown in Figure 5.

Table 24: Proportion of Patients with an ACR Response

IV RA Study 1 Active RA, despite MTX			
	Placebo + MTX	**SIMPONI® I.V. + MTX**	**95% CI[a]**
N[b]	197	395	
ACR 20			
Week 14	25%	59%	25.9, 41.4
Week 24	32%	63%	23.3, 39.4
ACR 50			
Week 14	9%	30%	15.3, 27.2
Week 24	13%	35%	15.1, 28.4
ACR 70			
Week 14	3%	12%	5.3, 13.4

Week 24	4%	18%	8.8, 18.1
[a]For difference in proportions [b]N reflects randomized patients.			

Figure 5: IV RA Study 1: Percent of Patients Achieving ACR 20 Response Over Time: Randomized Patients



The analysis is based on the intent-to-treat population. Last observation carried forward was performed for missing data. Patients who discontinued treatment due to lack of efficacy were counted as non-responders, as were patients who started prohibited medication or failed to achieve at least a 10% improvement in joint counts at Week 16.

The improvement in all components of the ACR response criteria for the SIMPONI® I.V. + MTX group was greater compared to the placebo + MTX group in RA IV Study 1 as shown in Table 25.

Table 25: Components of ACR Response at Week 14

	IV RA Study 1 Active RA, despite MTX	
	Placebo + MTX Mean (range)	**SIMPONI® I.V. + MTX Mean (range)**
N[a]	197	395
Number of swollen joints (0-66)		
Baseline	15 (5, 47)	15 (4, 56)
Week 14	11 (0, 41)	6 (0, 37)
Number of tender joints (0-68)		
Baseline	26 (6, 68)	26 (5, 68)
Week 14	20 (0, 68)	13 (0, 68)
Patient's assessment of pain (0-10)		
Baseline	6.5 (0.3, 10.0)	6.5 (1.3, 10.0)
Week 14	5.6 (0.2, 10.0)	3.9 (0.1, 9.6)
Patient's global assessment of disease activity (0-10)		
Baseline	6.5 (0.7, 10.0)	6.5 (1.4, 10.0)
Week 14	5.5 (0.4, 10.0)	4.0 (0.1, 9.6)
Physician's global assessment of disease activity (0-10)		
Baseline	6.3 (0.2, 9.5)	6.2 (1.5, 10.0)
Week 14	4.9 (0.1, 9.3)	3.1 (0.0, 8.2)
HAQ score (0-3)		
Baseline	1.6 (0.0, 3.0)	1.6 (0.0, 3.0)
Week 14	1.4 (0.0, 3.0)	1.1 (0.0, 3.0)
CRP (mg/dL) (0-1)		
Baseline	2.2 (0.02, 10.60)	2.8 (0.07. 21.10)
Week 14	1.8 (0.02, 10.50)	0.9 (0.02, 12.00)

Note: All values are means.
[a] N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.

At Week 14, a greater proportion of patients treated with SIMPONI® I.V. + MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 compared with the placebo + MTX group (15% compared to 5%; 95% confidence interval for difference [6.3%, 15.5%]).

Radiographic Response

In IV RA Study 1, structural joint damage was assessed radiographically and expressed as a change in van der Heijde-Modified Sharp Score (vdH-S) and its components, the erosion score and Joint Space Narrowing (JSN) score, at Week 24 compared to baseline. The SIMPONI® I.V. + MTX treatment group inhibited the progression of structural damage compared with placebo + MTX, as assessed by total vdH-S score as shown in Table 26.

Table 26: Radiographic Change From Baseline at Week 24

	Placebo + MTX (N=197)[a]	SIMPONI® I.V. + MTX (N=395)[a,b]
	Mean	**Mean**
Change Total vdH-S Score	1.1	0.03*
Change Erosion Score	0.5	-0.1
Change JSN Score	0.6	0.1

[a] N reflects randomized patients
[b] p-value is displayed only for the major secondary endpoint
* p≤0.001

At Week 24, a greater proportion of patients in the SIMPONI® I.V. + MTX group (71%) had no progression of structural damage (change in the total vdH-S score ≤ 0), compared to 57% of patients in the placebo + MTX group. At Week 52, the mean change from baseline in total vdH-S score was 1.2 in patients originally randomized to placebo + MTX who crossed over to SIMPONI® I.V. + MTX at Week 16 or 24, and 0.1 in patients originally randomized to SIMPONI® I.V.+ MTX who remained on active treatment.

Physical Function Response in Patients with RA

Physical function was assessed by the disability index of the Health Assessment Questionnaire (HAQ-DI). At Week 14, the SIMPONI® I.V.+ MTX group showed greater mean improvement in the HAQ-DI compared with placebo + MTX (0.5 compared to 0.2; 95% confidence interval for difference [0.2, 0.4]).

Psoriatic Arthritis

Study Demographics and Trial Design

The efficacy and safety of SIMPONI® I.V. were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial, IV PsA Study (GO-VIBRANT), in 480 adults with active psoriatic arthritis despite NSAID or DMARD therapy. Patients in this trial had a diagnosis of PsA for at least six months and had symptoms of active disease [≥5 swollen joints and ≥5 tender joints and a CRP level of ≥0.6 mg/dL]. Patients were randomized to receive SIMPONI® I.V. 2 mg/kg (N=241) or placebo (N=239) as a 30-minute intravenous infusion at Weeks 0, 4, 12 and 20. All patients on placebo received SIMPONI® I.V. at Week 24, Week 28 and every 8 weeks thereafter through Week 52. Patients in the group treated with SIMPONI® I.V. continued to receive infusions of SIMPONI® I.V. at Week 28 and every 8 weeks through Week 52. Previous treatment with a biologic was not allowed.

Patients were allowed to continue stable doses of MTX, NSAIDs, and low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone per day) during the study. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

Patients with each subtype of PsA were enrolled, including polyarticular arthritis with absence of rheumatoid nodules (44%), asymmetric peripheral arthritis (19%), distal interphalangeal joint involvement (8.1%), spondylitis with peripheral arthritis (25%), and arthritis mutilans (4.8%). The median duration of PsA disease was 3.5 years, 86% of patients had previously used MTX, and 35% of patients received at least one other DMARD in the past. At baseline, 76% and 54% of the patients had enthesitis and dactylitis, respectively. During the trial, the use of concomitant medications was MTX (70%), oral corticosteroids (28%), and NSAIDs (71%).

The primary endpoint was the percentage of patients achieving an ACR 20 response at Week 14. The major secondary endpoints were change in baseline in the HAQ-DI score at Week 14, the proportion of subjects who achieve an ACR 50 response at Week 14, the proportion of subjects (with baseline ≥3% Body Surface Area (BSA) psoriatic involvement) who achieve a PASI 75 response at Week 14, the change from baseline in total modified vdH-S score at Week 24, and the change from baseline in SF-36 PCS and MCS at Week 14.

TABLE 27: Summary of the Controlled Clinical Trial Supporting Efficacy in Patients with PsA

Study #	Trial Design	Dosage: Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
IV PSA Study (GO-VIBRANT)	Multicentre, double-blind, randomized, placebo-controlled	SIMPONI® I.V. 2 mg/kg infusion at Week 0, 4, and every 8 weeks thereafter for 24 weeks	241	46 (19, 69)	113 (46.9%)
		Placebo Placebo I.V, at Weeks 0, 4, 12 and 20.	239	47 (18, 79)	118 (49.4%)

Study Results

Reduction of Signs and Symptoms

Patients treated with SIMPONI® I.V. compared with placebo, achieved significant improvements in signs and symptoms as demonstrated by the percentage of patients with an ACR 20 response at Week 14 (see Table 28). This benefit was consistently observed when assessed in SIMPONI® I.V. -treated patients across the five PsA subtypes. ACR 20 responses observed in the SIMPONI® I.V.-treated groups were similar in patients who were or were not receiving concomitant MTX.

TABLE 28: IV PsA Study – Percentage of Patients with ACR Responses at Weeks 14 and 24			
	Placebo	**SIMPONI® I.V.**	**Treatment difference (95% CI) p-value**
	(N=239)	**(N=241)**	
ACR 20 response			
Week 14	52 (21.8%)	181 (75.1%)	53% (46%, 61%) $p < 0.001$[a]
ACR 50 response			
Week 14	15 (6.3%)	105 (43.6%)	37% (30%, 44%) $p < 0.001$[a]
Week 24	15 (6.3%)	129 (53.5%)	47% (40%, 54%) $p < 0.001$[a]
ACR 70 response			
Week 14	5 (2.1%)	59 (24.5%)	22% (17%, 28%) $p < 0.001$[a]

ACR: American College of Rheumatology
[a] to control the overall Type I error rate at the 0.05 significance level, the endpoints were tested using a hierarchical testing strategy

The percentage of patients achieving ACR 20 responses by visit through Week 24 is shown in Figure 6. The onset of action of SIMPONI® I.V. occurred as early as Week 2.

Figure 6: IV PsA Study: Percentage of Patients Achieving ACR 20 Through Week 24

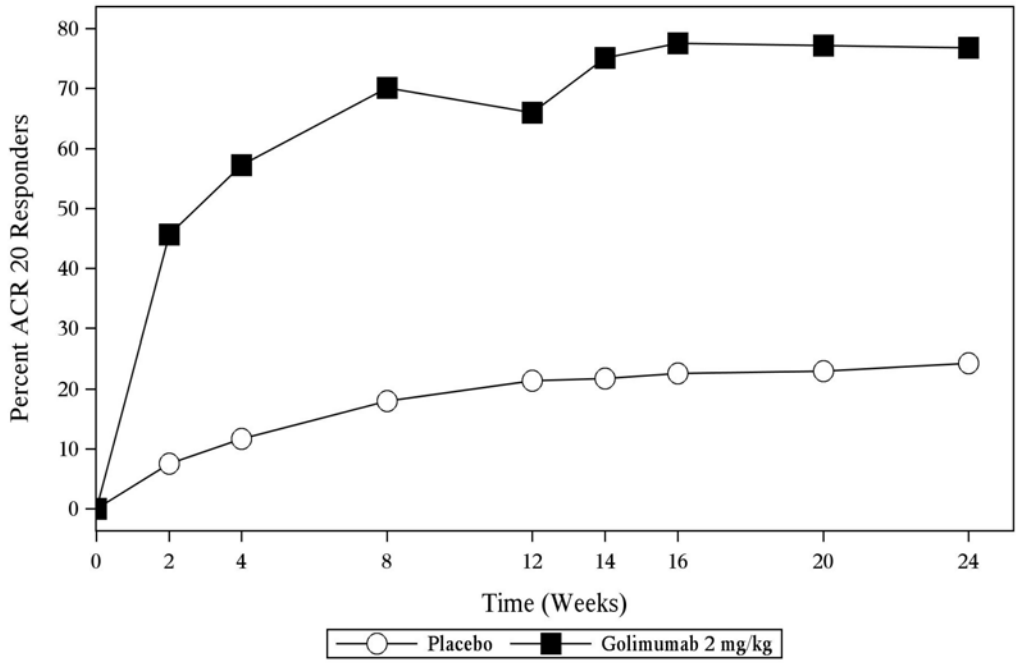


Table 29 shows the improvement in the individual components of the ACR response criteria for SIMPONI® I.V. and the placebo group at Weeks 14.

Table 29: IV PsA Study: Mean Changes in ACR Components at Week 14

	Placebo N=239[a]		**SIMPONI® I.V. N=241[a]**	
	Baseline	Week 14 change from baseline	Baseline	Week 14 change from baseline
ACR Components				
Number of swollen joints (0-66)	14	-2.9	14	-11
Number of tender joints (0-68)	26	-4.2	25	-15
Patient's assessment of pain (0-100 mm)	64	-11	63	-31
Patient global assessment of disease activity (0-100 mm)	63	-11	65	-32
Physician global assessment of disease activity (0-100 mm)	64	-13	62	-39
Disability Index (HAQ) (0-3)[b]	1.3	-0.13	1.3	-0.60
CRP (mg/L)[c]	20	-2.9	19	-16

Note: All values are means.
[a] N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.
[b] Health Assessment Questionnaire-Disability Index.
[c] CRP = C-reactive protein

Patients with enthesitis at baseline were evaluated for improvement using the Leeds Enthesitis Index (LEI) on a scale of 0-6. SIMPONI® I.V.-treated patients showed a median improvement in LEI score of 2.0 as compared with a median improvement in placebo-treated patients of 0.0 at Week 14 ($p<0.001$). Patients with dactylitis at baseline were evaluated for improvement on a scale of 0-60. SIMPONI® I.V.-treated patients showed a median improvement in dactylitis score of 4.0 compared with a median improvement of 2.0 in placebo-treated patients at Week 14 ($p<0.001$).

Psoriasis Skin Response

Among patients with ≥ 3% BSA psoriasis skin involvement at baseline (82%), a significantly greater percentage of patients achieved Psoriatic Area Severity Index 75 (PASI 75) response at Week 14 when treated with SIMPONI® I.V. compared with placebo (59% vs 14%, $p<0.001$).

Radiographic Response

In the IV PsA Study, structural joint damage was assessed radiographically and expressed as a change in total modified vdH-S score at Week 24 compared to baseline. SIMPONI® I.V. inhibited the progression of structural damage compared with placebo, as assessed by total modified vdH-S score (-0.4 vs 2.0; $p<0.001$).

At Week 24, the proportion of patients who had no progression of structural damage (change in the total modified vdH-S score ≤ 0) was 72% in the SIMPONI® I.V. group and 43% in the placebo group.

Physical Function and Response

Improvement in physical function as assessed by HAQ-DI at Week 14 showed a significantly greater mean decrease (improvement) from baseline in HAQ-DI score in the SIMPONI® I.V. group compared with placebo.

Other Health Related Outcomes

General health status was assessed by the 36-item Short Form Health Survey (SF-36). Patients receiving SIMPONI® I.V. demonstrated a statistically significantly greater mean increase (i.e. improvement) from baseline compared with placebo in the physical and mental component summaries at Week 14.

Ankylosing Spondylitis

Study Demographics and Trial Design

The efficacy and safety of SIMPONI® I.V. were evaluated in a multicenter, randomized, double-blind, placebo-controlled trial, IV AS Study (GO-ALIVE) in 208 adults with active ankylosing spondylitis and inadequate response or intolerance to NSAIDs. Patients had a diagnosis of definite AS for at least 3 months according to modified New York criteria. Patients had symptoms of active disease [Bath AS Disease Activity Index (BASDAI) ≥ 4, VAS for total back pain of ≥ 4, on scales of 0 to 10 cm (0 to 100 mm), and a hsCRP level of ≥ 0.3 mg/dL (3 mg/L)]. Patients were randomized to receive SIMPONI® I.V. 2 mg/kg (N=105) or placebo (N=103) as a 30-minute intravenous infusion at Weeks 0, 4 and 12. All patients on placebo received SIMPONI® I.V. at Week 16, Week 20 and every 8 weeks thereafter through Week 52. Patients in the SIMPONI® I.V. treatment group continued to receive SIMPONI® I.V. infusions at Week 20 and every 8 weeks through Week 52. Patients were allowed to continue stable doses of concomitant MTX, SSZ, hydroxychloroquine (HCQ), low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone per day), and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint was the percentage of patients achieving an Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 16.

In the IV AS Study, the median duration of AS disease was 2.8 years, median duration of inflammatory back pain was 8 years, 90% were HLA-B27 positive, 8.2% had prior joint surgery or procedure, 5.8% had complete ankylosis of the spine, 14% had received prior therapy with one biologic TNF blocker (other than golimumab) and discontinued for reasons other than lack of efficacy within the first 16 weeks of treatment (primary failure), and 76% received at least one

DMARD in the past. During the trial, the use of concomitant medications was NSAIDs (88%), SSZ (38%), corticosteroids (26%), MTX (18%), and HCQ (0.5%).

TABLE 30: Summary of the Controlled Clinical Trial Supporting Efficacy in Patients with AS

Study #	Trial Design	Dosage: Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Gender (% Female)
IV AS Study (GO-ALIVE)	Multicentre, double-blind, randomized, placebo-controlled	SIMPONI® I.V. 2 mg/kg infusion at Week 0, 4, and every 8 weeks thereafter	105	38 (19, 64)	19 (18.1%)
		Placebo Placebo I.V. at Weeks 0, 4 and 12	103	39 (20, 67)	26 (25.2%)

Clinical Response

Patients treated with SIMPONI® I.V. compared with placebo, achieved significant improvements in signs and symptoms as demonstrated by the percentage of patients with an ASAS 20 response at Week 16 (see Table 31).

TABLE 31: IV AS Study - Percentage of ASAS Responders at Weeks 16

	Placebo N =103	SIMPONI® I.V. N =105	Treatment Difference (95% CI) p-value
ASAS 20 response % (n)	27 (26.2%)	77 (73.3%)	47% (35%, 59%) p<0.001[a]
ASAS 40 response % (n)	9 (8.7%)	50 (48.0%)	39% (28%, 50%) p<0.001[a]

[a] to control the overall Type I error rate at the 0.05 significance level, the endpoints were tested using a hierarchical testing strategy

The percentage of patients achieving ASAS 20 responses by visit through Week 16 for Trial AS is shown in Figure 7. The onset of action of SIMPONI® I.V. occurred as early as Week 2.

Figure 7: Percentage of Patients Achieving an ASAS 20 Response Through Week 16

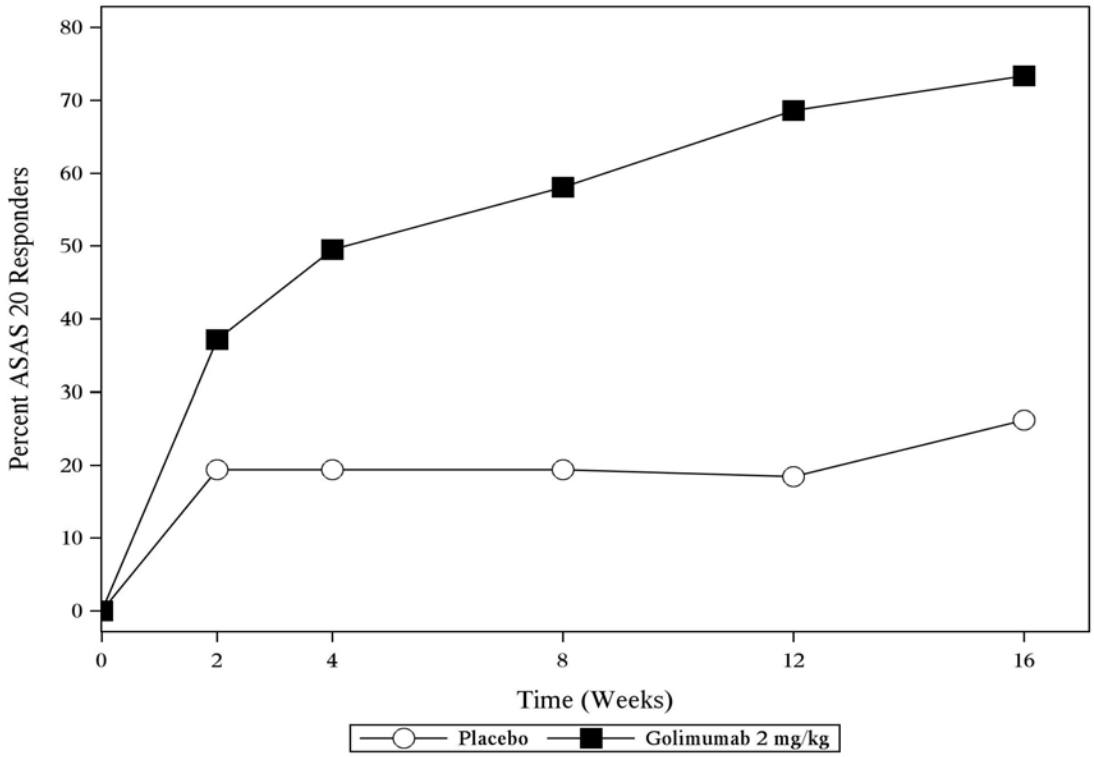


Table 32 shows the improvement in the components of the ASAS response criteria and other measures of disease activity for the SIMPONI® I.V. and placebo-treated patients.

Table 32: IV AS Study: Mean Change from Baseline in ASAS 20 Components and Other Measures of Disease Activity at Week 16

	Placebo N=103[a]		**SIMPONI® I.V.** N=105[a]	
	Baseline	Week 16 change from baseline	Baseline	Week 16 change from baseline
ASAS 20 Response criteria				
Patient Global Assessment of Disease Activity (0-100 mm)[b]	71	-8.3	73	-34
Total back pain (0-100 mm)[c]	73	-12	72	-32
BASFI (0-10)[d]	6.1	-0.5	6.3	-2.4*
Inflammation (0-10)[e]	7.4	-1.1	7.3	-3.6
BASDAI Score	7.1	-1.1	7.1	-3.1
BASMI[f]	5.0	-0.1	5.0	-0.4*
hsCRP (mg/L)	19	-2.3	20	-17

* $p<0.001$
[a] N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.
[b] Measured on a Visual Analog Scale (VAS) with 0= very well, 100=very poor
[c] Measured on a Visual Analog Scale (VAS) with 0= no pain, 100=most severe pain
[d] BASFI is Bath Ankylosing Spondylitis Functional Index.
[e] Inflammation is the mean of 2 morning stiffness self-assessments in the BASDAI (Bath AS Disease Activity Index).
[f] BASMI is Bath Ankylosing Spondylitis Metrology Index

At Week 16, a significantly greater percentage of patients treated with SIMPONI® I.V. achieved a low level of disease activity (<2 [on a scale of 0 to 10 cm] in all four ASAS domains) compared with patients treated with placebo (16.2% vs. 3.9%).

Other Health-Related Outcomes

General health status was assessed by the 36-item Short Form Health Survey (SF-36). Patients receiving SIMPONI® I.V. demonstrated a significantly greater mean improvement from baseline compared with placebo in physical component summary and mental component summary scores.

Patients treated with SIMPONI® I.V. achieved significantly greater mean decrease (improvement) from baseline in the Ankylosing Spondylitis Quality of Life questionnaire (ASQoL) compared to placebo-treated patients at Week 16.

DETAILED PHARMACOLOGY

The binding of human TNF by golimumab was shown to neutralize TNF-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab. Consistent with other human IgG1 antibodies, golimumab is capable of binding to Fc receptors and activating complement. However, no golimumab-mediated cell lysis was seen with lipopolysaccharide (LPS)-stimulated human monocytes upon addition of complement or effector cells. In addition, no golimumab-induced apoptosis was detected with LPS-stimulated human peripheral blood mononuclear cells.

The effect of golimumab *in vivo* was tested in a human TNF transgenic mouse model of experimental arthritis. Golimumab treatment produced a statistically significant delay in the onset of clinical symptoms compared with untreated mice, as well as a significant reduction in joint pathology.

Absorption

Following a single SC administration of SIMPONI® to healthy subjects or patients with RA, the time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A SC injection of 50 mg SIMPONI® to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.2 ±1.4 μg/mL. Both Cmax and area under the concentration-time curve (AUC) increased proportionally with doses over the range of 50 to 400 mg following a single SC administration.

Following a single SC injection of 100 mg in healthy subjects, the absorption of SIMPONI® was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since SIMPONI® exhibited approximately dose proportional PK following SC administration, the absolute bioavailability of a SIMPONI® 50 mg or 200 mg dose is expected to be similar to the 100 mg dose.

Following a single IV administration of 2 mg/kg SIMPONI® I.V., a mean C_{max} of 44.4 ±11.3 μg/mL was observed in patients with RA.

Distribution

Following a single IV administration, the mean volume of distribution was estimated to be 115 ± 19 mL/kg in healthy subjects, and 151 ± 61 mL/kg in patients with RA. The volume of distribution for SIMPONI® indicates that SIMPONI® is distributed primarily in the circulatory system with limited extravascular distribution.

Metabolism

The exact metabolic pathway of SIMPONI® is unknown.

Elimination

Following a single IV administration, the systemic clearance of SIMPONI® was estimated to be 6.9 ± 2.0 mL/day/kg in healthy subjects and 7.6 ± 2.0 mL/day/kg in patients with RA.

Terminal half-life was consistent between IV and SC administration of SIMPONI®. The terminal half-life was estimated to be 12 ± 3 days in healthy subjects and similar half-life was observed in patients with RA, PsA, AS, or UC.

After a 6-month treatment with SIMPONI® by subcutaneous administration in patients with RA, concomitant use of methotrexate reduced the apparent clearance of SIMPONI® by 36%; however, following IV administration, no appreciable effect of methotrexate on the clearance of SIMPONI® was observed. Population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of SIMPONI® following SC administration.

Population PK analyses showed that, following SC administration of SIMPONI®, patients with higher C-reactive protein levels tended to have higher apparent clearance of SIMPONI®. Patients with higher C-reactive protein levels were more likely to have lower trough serum concentrations of SIMPONI® following SC administration of SIMPONI®. In contrast, C-reactive protein level showed no effect on the clearance of SIMPONI® following IV administrations of 2 mg/kg SIMPONI® at Weeks 0, 4, and every 8 weeks thereafter.

Patients who developed anti-SIMPONI® antibodies following SC or IV administration generally had low trough steady-state serum concentrations of SIMPONI®.

TOXICOLOGY

Nonclinical toxicology studies include multiple-dose IV studies and single-dose and multiple-dose SC studies of up to 6 months duration, an embryo-fetal development study evaluating the maternal and fetal effects of golimumab treatment during pregnancy, and a prenatal and postnatal development study evaluating the maternal and neonatal effects of golimumab treatment during pregnancy and lactation. The developmental and reproductive toxicity of an analogous anti-mouse TNFα monoclonal antibody (mAb), cV1q, was also assessed and are included as additional supportive data for the development of golimumab. An *in vitro* human tissue cross-reactivity study was also conducted.

Results from nonclinical toxicology studies are summarized in Table 33.

Repeated Dose Toxicology Studies

Three repeated dose toxicity studies were conducted to support golimumab administration in patients. In the 6-month IV study, no abnormal findings considered golimumab-related were revealed at necropsy, except for a disseminated histoplasmosis infection found in one animal in the 25 mg/kg recovery group. This finding is not unexpected, as opportunistic infections are

known risks of anti-TNF inhibitors and have been observed in human subjects treated with anti-TNF agents. In both the 6-month IV study and the 6-month SC study, there was a slight increase in the number of circulating lymphocytes. In the 6-month IV study there was a slight decrease in the humoral immune response to KLH. This reduction was not observed in the 6-month SC study where a different immunization protocol was used. The lymphocyte changes and slight reduction in immune response to KLH immunization are considered to be biological responses to TNFα inhibition and are not considered to be of toxicological significance.

Developmental and Reproductive Toxicity Studies
Golimumab administration to cynomolgus monkeys during pregnancy and lactation produced no adverse developmental effects, including no effects on the developing immune system. Fetuses were exposed to golimumab during gestation. In fetuses, golimumab acquired during gestation persisted in the infant serum for at least 6 months after birth. Golimumab was detected in the breast milk at concentrations that were approximately 350-fold lower than in the maternal serum concentrations.

In the mouse studies using cV1q, no toxicologically significant effects of anti-TNFα mAb treatment were detected on fertility, embryo-fetal, pre- and post-natal development and developmental immunotoxicity.

Genotoxicity
Genotoxicity studies have not been conducted with golimumab. Because of their large molecular size, mAbs are not expected to pass through the cellular and nuclear membranes and are not expected to gain access to or to interact with DNA or other chromosomal material.

Carcinogenicity
No carcinogenicity studies have been performed with golimumab.

TABLE 33: Nonclinical toxicology studies with golimumab or with anti-mouse TNFα monoclonal antibody (cV1q)

Study Number	Species (study type)	Route of Administration, Dose/Dosage and/or Concentration	Results
T-2000-004	Human tissue (*in vitro* tissue cross reactivity) (GLP)	Golimumab (cell line 466D) 1, 10, and 200 µg/mL Tissues from 3 human donors	Golimumab did not react with the majority of the normal human tissues evaluated. Slight to moderate reactivity (staining) of the adnexal epithelium of the skin from 2 of 3 donors and slight staining of the keratinocytes in the epidermis (stratum malpighii) of nipple skin overlying the breast (mammary gland) from 1 of 3 donors.
T-2000-007	Cynomolgus monkeys (1-month IV subchronic toxicity) (GLP)	Golimumab (cell line 466D) 0, 10, and 50 mg/kg IV Once weekly for 4 weeks 5 males and 5 females/group	Golimumab produced no treatment related effects on body weight, food consumption, physical examinations, clinical observations, ophthalmic examinations, ECG, and clinical and anatomic pathology. Golimumab had no effects on immunotoxicity evaluated by lymphocyte subsets analysis, humoral immune response to KLH immunization (100 µg IM in incomplete Freund's adjuvant on Days 8 and 22), and immunohistopathology of lymphoid organs (CD3,

TABLE 33: Nonclinical toxicology studies with golimumab or with anti-mouse TNFα monoclonal antibody (cV1q)			
Study Number	**Species (study type)**	**Route of Administration, Dose/Dosage and/or Concentration**	**Results**
			CD20 cells). The NOAEL was at least 50 mg/kg. The C_{max} at the NOAEL was 2,428 µg/mL in males and 2468 µg/mL in females.
T-2004-006	Cynomolgus monkeys (6-month IV chronic toxicity) (GLP)	Golimumab (cell line C524A) 0, 25, and 50 mg/kg IV Once weekly for 13 or 25 weeks 8 males and 8 females/group	Golimumab produced no treatment-related effects on body weight, food, consumption, physical examinations, ECGs, clinical observations, ophthalmic examinations and clinical pathology. The only possibly treatment-related anatomic pathology finding was a single case of disseminated histoplasmosis infection in one animal treated with 25 mg/kg and necropsied 3 months after the last dose. Immunotoxicity was evaluated by lymphocyte subset analysis (CD3, CD20, CD4, CD8, CD14, CD16, CD44, CD45A), humoral immune response (KLH 10 mg IM) and immunohistopathology of lymphoid organs (CD3, CD20). Golimumab treatment resulted in a slight increase in peripheral blood lymphocytes and a slight reduction in the humoral immune response to KLH. These small changes are not considered to be of toxicological significance. There was no golimumab treatment-related effect on immunohistopathology of lymphoid tissues. The NOAEL was at least 50 mg/kg. The C_{max} at the NOAEL was 2,819 µg/mL in males and 2437 µg/mL in females.
T-098-004	Mice (6-month IV chronic toxicity) (GLP)	CV1q 0, 10, 40 mg/kg IV Once weekly for 13 or 25 weeks 40 males and 40 females/group	There were no effects of cV1q treatment on clinical observations, body weight, food consumption, ophthalmology, serum chemistry, or hematology evaluations. There were no pathological findings observed considered cV1q treatment-related.
T-2000-008	Cynomolgus monkeys (single-dose SC local tolerance) (GLP)	Golimumab (cell line 466D) 10 mg/kg Human immune globulin (IGIV) 3.0 mg/kg	Golimumab was well tolerated at a single SC dose of 10 mg/kg. Macroscopic observations of local irritation (erythema, edema and heat) in golimumab-treated animals were similar to those following SC injection of IGIV.
T-2000-009	Cynomolgus monkeys (1-month SC local tolerance) (GLP)	Golimumab (cell line 466D) 10 mg/kg Human immune globulin (IGIV) 3.0 mg/kg Twice weekly for 4 weeks	Golimumab was well tolerated at multiple SC doses of 10 mg/kg. Macroscopic observations of local irritation (erythema, edema and heat) in golimumab-treated animals were similar to those following SC injection of IGIV.

TABLE 33: Nonclinical toxicology studies with golimumab or with anti-mouse TNFα monoclonal antibody (cV1q)			
Study Number	**Species (study type)**	**Route of Administration, Dose/Dosage and/or Concentration**	**Results**
T-2002-001	Cynomolgus monkeys (6-month SC chronic toxicity) (GLP)	Golimumab (cell line C524A) 0, 25, 50 mg/kg Twice weekly for 13 or 26 weeks 8 males and 8 females/group	Golimumab produced no treatment-related effects on body weight, food consumption, physical examinations, ECGs, clinical observations, ophthalmic examinations and clinical and anatomic pathology. Immunotoxicity was evaluated by lymphocyte subset analysis (CD3, CD20, CD4, CD8, CD14, CD16, CD44, CD45A), humoral immune response (KLH 100 µg IM in incomplete Freund's adjuvant on Days 12 and 30) and immunohistopathology of lymphoid organs (CD3, CD20). Golimumab treatment resulted in a slight increase in peripheral blood lymphocytes that was not considered of toxicological significance. There was no golimumab treatment-related effect on KLH antibody titers or on immunohistopathology of the lymphoid tissues. The NOAEL was at least 50 mg/kg. The C_{max} at the NOAEL was 2,492 µg/mL in males and 2427 µg/mL in females.
Developmental and Reproductive Studies			
T-2003-005	Cynomolgus monkeys (embryo-fetal development) (GLP)	Golimumab (cell line C524A) 0, 25, 50 mg/kg SC Twice weekly from Gestation Day (GD) 20 to GD 51 (period or organogenesis) 12-14 pregnant females/group	Fetuses were harvested by cesarean section on GD100 and were examined for any developmental abnormalities. Potential effects on fetal immune system development were evaluated by analysis of cord blood lymphocyte subsets and immunohistopathology of fetal lymphoid organs. Golimumab produced no treatment-related effects on the dams or on the fetuses. The NOAEL was at least 50 mg/kg. Maternal C_{max} at the NOAEL was 1,576 µg/mL. GD100 serum concentrations at the NOAEL were 62 µg/mL in the dams and 32 µg/mL in the fetuses.
T-2004-007	Cynomolgus monkeys (pre- and post-natal development) (GLP)	Golimumab (cell line C524A) 0, 25, 50 mg/kg SC Twice weekly form GD 50 through Lactation Day (LD) 33 12 pregnant females/group	Infants (F1 generation) were examined from birth (approximately GD165) through 6 months of age for morphological and functional development, body weight, food consumption, ECG, ophthalmology and clinical pathology. A full gross anatomic pathology and limited microscopic pathology examinations were conducted on infants at 6–8 months of age. Immune function in the neonates was determined at 6 months of age by humoral immune response to tetanus toxoid (TTX, 6 Lf IM) and KLH (2 mg/kg SC) immunizations and Delayed Type Hypersensitivity (DTH) dermal responses to intracutaneous injection of TTX. **Golimumab produced no treatment-related effects on the dams or on the infants.** The NOAEL was at least 50 mg/kg.

TABLE 33: Nonclinical toxicology studies with golimumab or with anti-mouse TNFα monoclonal antibody (cV1q)			
Study Number	**Species (study type)**	**Route of Administration, Dose/Dosage and/or Concentration**	**Results**
			Maternal Cmax at the NOAEL was 1,482 µg/mL. **Breast milk concentration on LD28 was 3.6 µg/mL.** **Golimumab was detectable in infant serum through 6 months of age.**
T-098-003	Mice (male and female fertility) (GLP)	cV1q 0, 10 and 40 mg/kg IV Males: once weekly beginning 56 days (8 weeks) before cohabitation and continuing through cohabitation (2 weeks) and the week before sacrifice. Females: beginning 2 weeks before cohabitation and on GD 0 and 7.	cV1q produced no treatment-related effects on fertility and general reproduction.
T-096-011	Mice (embryo-fetal development) (GLP)	cV1q 0, 10 40 mg/kg IV GD 6 and GD 12	cV1q produced no maternal or developmental toxicity.
T-2001-002	Mice (pre- and post-natal development) (GLP)	cV1q 0, 10, 40 mg/kg IV GD 6, 12, 18 and LD 3, 9, 15	cV1q produced no maternal or developmental toxicity in the F1 generation mice, including no effects on postweaning behavioural/functional and reproduction/development evaluations. Immunotoxcity parameters evaluated in the F1 generation at 11 weeks of age showed no treatment-related effects, with the exception of a slight, non-toxicologically significant, decrease in humoral immune response to SRBC immunization in the 40 mg/kg treated females.
T-2003-013	Mice (developmental immunotoxicity) (GLP)	CV1q 0, 40 mg/kg IV GD 6, 12, and 18 or GD 6, 12, 18 and LD 3, 9, 15	cV1q produced no maternal or developmental toxicity in the F1 generation mice and no treatment-related effects on immunotoxicity parameters, including no effects on humoral immune response to SRBC immunization.

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PART III: CONSUMER INFORMATION

SIMPONI®
pronounced sim poe NEE
golimumab injection
Single-use Autoinjector

This leaflet is part III of a three-part "Product Monograph" published when SIMPONI® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SIMPONI®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the Medication Is Used For:
SIMPONI® is a prescription medicine that is approved for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and ulcerative colitis. In these diseases, the body produces too much of a substance called tumour necrosis factor alpha (TNF-alpha). Too much of this substance causes your body's immune system to attack healthy tissue and results in inflammation. Blocking TNF-alpha with SIMPONI® can reduce inflammation associated with these diseases, but can also reduce your immune system's ability to fight off infections.

Rheumatoid Arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis, you will be given SIMPONI®, which you will take in combination with methotrexate. In patients with rheumatoid arthritis, SIMPONI® may help reduce signs and symptoms of inflammatory arthritis (such as pain), may help improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), and may help prevent damage to your bones and joints.

Psoriatic Arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis, you will be given SIMPONI® alone or in combination with methotrexate. In patients with psoriatic arthritis, SIMPONI® may help reduce signs and symptoms of inflammatory arthritis (such as pain), may help improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), and may help to prevent damage to your bones and joints.

Ankylosing Spondylitis
Ankylosing spondylitis is an inflammatory disease of the spine. If you have active ankylosing spondylitis, you will be given SIMPONI® to reduce the signs and symptoms of your disease.

Non-radiographic axial spondyloarthritis
Non-radiographic axial spondyloarthritis is an inflammatory disease of the spine. If you have severe, active non-radiographic axial spondyloarthritis, you will be given SIMPONI® to reduce the signs and symptoms of your disease.

Ulcerative Colitis
Ulcerative colitis (UC) is a chronic inflammatory bowel disorder. In patients with ulcerative colitis, SIMPONI® may
- Reduce the signs and symptoms of your disease
- Induce remission of your disease
- Induce intestinal healing
- Improve your quality of life by helping you feel better
- Maintain control of signs and symptoms of your disease
- Achieve long term remission of your disease

What it Does:
SIMPONI® is a medicine that affects your immune system. SIMPONI® can lower the ability of your immune system to fight infections. Some patients have had serious infections while receiving SIMPONI®, including tuberculosis, and systemic bacterial, and fungal, infections. Some patients have died from these serious infections.

When it Should Not Be Used:
SIMPONI® is a clear to slightly clear, colourless to light yellow solution. This appearance is not unusual for solutions containing protein.
SIMPONI® should not be used:
- after the expiration date on the label
- if the product is damaged
- if the liquid is discoloured, cloudy or you can see other particulate matter floating in it
- if you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated)

SIMPONI® should not be used if you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.

SIMPONI® should not be used if you have heart failure that is moderate or severe.

SIMPONI® should not be used by patients who are allergic to golimumab, latex or any other ingredient (polysorbate 80 or sorbitol) in the formulation or component of the container.

What the Medicinal Ingredient Is:
Golimumab

What the Important Nonmedicinal Ingredients Are:
L-histidine
L-histidine hydrochloride
Polysorbate 80
Sorbitol
Water for injection

No preservatives are present.

What Dosage Forms it Comes In:
SIMPONI® is available as a single-use autoinjector and as a single-use pre-filled syringe.
Each single-use autoinjector contains either 50 mg golimumab per 0.5 mL, or 100 mg golimumab per 1 mL.

Each single-use pre-filled syringe contains either 50 mg golimumab per 0.5 mL, or 100 mg golimumab per 1 mL.

Where I May Receive Training on How to Self-Inject SIMPONI®: The BioAdvance® Network has been established to offer training on how to self-inject SIMPONI®. Patients can be trained by BioAdvance® qualified healthcare professionals either at their home or at BioAdvance® clinics located across Canada. Contact your doctor if you have any questions.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal and bacterial infections), have been reported in patients receiving SIMPONI® and other similar medicines. Some patients with these infections have died. Prior to treatment with SIMPONI®, you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by a fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or travelled. If you develop an infection during treatment with SIMPONI®, you should tell your doctor right away.

Prior to treatment with SIMPONI®, you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with SIMPONI®.

Treatment with SIMPONI® must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking SIMPONI® and for 6 months after you receive the medicine. If you need surgery, tell your doctor that you have taken SIMPONI®.

Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF blockers, of which SIMPONI® is a member.

BEFORE you use SIMPONI® talk to your doctor or pharmacist if you:

- have any kind of infection even if it is very minor
- have an infection that won't go away or a history of infection that keeps coming back
- have had TB (tuberculosis), or have recently been near anyone who might have TB. Your doctor will evaluate you for TB and perform a skin or blood test. If your doctor feels that you are at risk for TB, he or she may start treating you for TB before you begin SIMPONI® therapy
- have or have had a hepatitis B infection
- have heart failure, or if you previously had or currently have any heart condition. If you develop new or worsening symptoms of heart failure, such as shortness of breath or swelling of your feet, you must notify your doctor
- have or have had a condition that affects your nervous system, like multiple sclerosis or Guillain-Barré syndrome. You should tell your doctor if you experience weakness in your arms or legs, numbness, tingling, or visual disturbances
- have or have had any type of cancer
- have recently received or are scheduled to receive a vaccine
- have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- have a latex allergy
- are pregnant, planning to become pregnant, or breastfeeding. SIMPONI® should only be used during pregnancy if clearly needed. If you are being treated with SIMPONI®, you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last SIMPONI® injection. Women who are breastfeeding should talk to their doctor about whether or not to use SIMPONI®
- received SIMPONI® while you were pregnant as your baby may be at higher risk of getting an infection. It is Important to tell your baby's doctor and other health professionals about your SIMPONI® use before the baby receives any vaccine as certain vaccines may put your baby at higher risk of infections

What Are the Possible Side Effects with SIMPONI®?
Serious side effects that may require treatment can occur during SIMPONI® therapy. Possible serious side effects of SIMPONI® include:

Serious Infections
(See What it Does) If you develop a fever, chills, headache, flu-like symptoms, feel tired, have a cough, blood in your sputum, shortness of breath, night sweats, weight loss, nausea, vomiting, diarrhea, frequency or burning while passing urine, redness or swelling of skin or joint, cold sores, tooth pain or new or worsening of pain in any location while or after receiving SIMPONI®, you should tell your doctor right away because these could be signs that you are getting an infection.

Treatment with TNF-blocking agents such as SIMPONI® may result in reactivation of the hepatitis B virus in patients who carry this virus. If you know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with

SIMPONI®. Your doctor should do a blood test for hepatitis B virus before you start treatment with SIMPONI®.

Allergic Reactions
Some patients may get allergic reactions to SIMPONI®. Some reactions may be serious, and in rare instances, life-threatening. Some of these reactions occurred after the first administration of SIMPONI®. Symptoms of an allergic reaction may include hives, rash, difficulty breathing, chest pain, and high or low blood pressure. You should contact your doctor if you experience any of these symptoms.

Needle Cover with Dry Natural Rubber (a form of latex)
The needle cover on the pre-filled syringe and the autoinjector contains dry natural rubber (a form of latex). This may cause allergic reactions in people who are sensitive to latex. Tell your doctor if you have ever had an allergic reaction to latex or developed any allergic reaction to SIMPONI® injection.

Injection Site Reactions
Some patients develop reactions at the injection site at their skin after SIMPONI® injections. These reactions may include mild rash, swelling, bruising, hives, pain, numbness, and irritation. You should contact your doctor if you experience severe symptoms at injection site.

Cancer
In clinical studies, reports of blood cancer called lymphoma were more frequent in patients on SIMPONI® than expected for people in general. People who have been treated for rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis for a long time, particularly those with highly active disease may be more prone to develop lymphoma. Cancers, other than lymphoma, have also been reported in patients treated with SIMPONI® or other TNF-blockers. In a study of SIMPONI® in patients with severe, persistent asthma, cancers occurred in SIMPONI®-treated patients but not in control-treated patients. If you have severe, persistent asthma, you should discuss with your doctor whether SIMPONI® is appropriate for you. Some patients treated with SIMPONI® have developed certain kinds of skin cancer like melanoma. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.

Rarely, a specific and severe type of lymphoma called Hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers, of which SIMPONI® is a member. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and had also received drugs known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking IMURAN (azathioprine) or PURINETHOL (6-mercaptopurine) with SIMPONI®.

You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking SIMPONI®. Whether you decide to use SIMPONI® or not, you should discuss with your doctor the cancer screening measures and impact of lifestyle choices on the risk of developing cancer.

Congestive Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blocking agents, including SIMPONI®. Some of these patients died. SIMPONI® has not been studied in patients with CHF. Tell your doctor if you have heart failure. If you have mild heart failure and your doctor decides to administer SIMPONI®, your condition should be closely monitored during treatment. If you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet), you should contact your doctor right away.

Neurological Events
In rare instances patients treated with TNF-blocking agents may develop diseases such as multiple sclerosis or Guillain-Barré syndrome. Tell your doctor if you have a history of a neurological disease. If you develop symptoms of neurological disease, such as changes in your vision, weakness in your arms or legs, or numbness or tingling in any part of your body, you should contact your doctor right away.

Blood Problems
In some instances, patients treated with TNF-blocking agents may develop low blood counts. If you develop symptoms such as persistent fever, bleeding, or bruising, you should contact your doctor right away.

Vaccinations
You should not receive certain vaccines while using SIMPONI®. If you have recently received or are scheduled to receive a vaccine, please inform your doctor.

Certain vaccinations may cause infections. If you received SIMPONI® while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important to tell your baby's doctor and other health care professionals about your SIMPONI® use so they can decide when your baby should receive any vaccine.

Liver Problems
There have been cases where patients taking SIMPONI® developed liver problems. Signs that you could be having a problem include: skin and eyes turning yellow, dark brown-coloured urine, right-sided abdominal pain, fever, nausea, vomiting, and severe fatigue. You should contact your doctor right away if you experience these symptoms.

Driving and Using Machines
SIMPONI® may have a minor influence on your ability to drive and use machines. Dizziness may occur following administration of SIMPONI®. If this happens, do not drive or use any tools or

machines.

Check the Prescribed Strength
SIMPONI® is available in 50 mg and 100 mg strengths. When you receive your SIMPONI® make sure the strength matches what was prescribed to you by your doctor for your condition. Contact your doctor if you are not sure if you have received the correct strength.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take. These include any other medicines to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis.

Drugs that may interact with SIMPONI® include: prescription and non-prescription medicines, vitamins, and herbal supplements.

Tell your doctor if you take KINERET (anakinra) or ORENCIA (abatacept) or other immunosuppressant medications. SIMPONI® should not be taken together with anakinra or abatacept. Also, tell your doctor if you are taking other medications that affect your immune system.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine.

PROPER USE OF THIS MEDICATION

- For rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis SIMPONI® 50 mg is given by injection under the skin (subcutaneously) with an autoinjector or a pre-filled syringe once a month, on the same date each month.
- If you are receiving SIMPONI® for ulcerative colitis, all injections will be given subcutaneously. You will receive your first 200 mg dose followed by an additional 100 mg dose 2 weeks after the first dose. You will receive a 50 mg or 100 mg dose every 4 weeks thereafter as directed by your doctor.
- SIMPONI® is intended for use under the guidance and supervision of your doctor. Your doctor will tell you how often to take SIMPONI®. **Do not take SIMPONI® more often than prescribed**. If your doctor determines that it is appropriate, you may be able to administer SIMPONI® to yourself, after proper training in injection technique (**see** *INSTRUCTIONS FOR INJECTING SIMPONI® USING A SINGLE-USE SmartJect® AUTOINJECTOR*).
- If you take more SIMPONI® than you were told to take, call your doctor.
- Do not miss any doses of SIMPONI® (See *Missed Dose*).

Usual Dose:
Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Non-radiographic axial spondyloarthritis
50 mg of SIMPONI® given as a subcutaneous injection once a month, on the same date each month.

Ulcerative Colitis
200 mg of SIMPONI® given as a subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 50 or 100 mg every 4 weeks, thereafter. Your doctor may consider doing a blood test (therapeutic drug monitoring) to determine how much golimumab is in your blood stream in order to optimize your dose of SIMPONI®.

Overdose:
Single doses up to 10 mg/kg intravenously have been administered in a clinical study without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Patients who miss a dose of SIMPONI®, should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.

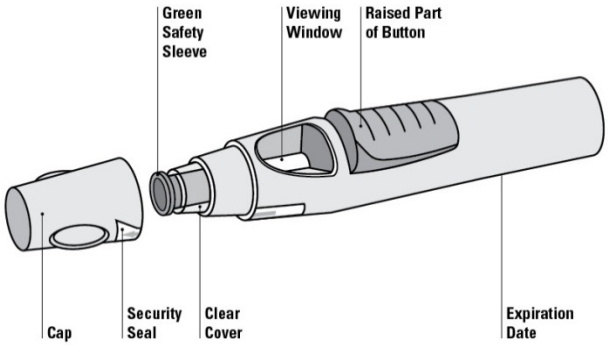
If you are not sure what to do, talk to your doctor or pharmacist.

INSTRUCTIONS FOR INJECTING SIMPONI® USING A SINGLE-USE SmartJect® AUTOINJECTOR

If you would like to self-inject SIMPONI®, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your healthcare professional to schedule a training session.

STEP 1: PREPARING TO USE THE SmartJect® AUTOINJECTOR

The diagram below shows what the autoinjector looks like:



DO NOT shake the autoinjector at any time.
DO NOT remove the autoinjector cap until instructed to do so.

Check Expiration Date

- Check the expiration date (indicated as "EXP") on the autoinjector
- You can also check the expiration date printed on the carton
- If the expiration date has passed, or if the autoinjector has been kept at room temperature 25ºC [77ºF] for longer than 30 days or if the autoinjector has been stored above 25ºC [77ºF], **DO NOT** use the autoinjector. Please contact your doctor or pharmacist or call 1-800-567-3331 (Canada only) for assistance

Check Security Seal

- Check the security seal around the cap of the autoinjector. If the security seal is broken, do not use the autoinjector and please contact your doctor or pharmacist or call 1-800-567-3331 (Canada only) for assistance

Wait 30 Minutes

- To ensure proper injection, allow the autoinjector to sit at room temperature outside the carton for 30 minutes out of the reach of children

DO NOT warm the autoinjector in any other way (for example, **DO NOT** warm it in a microwave or in hot water).
DO NOT remove the autoinjector cap while allowing it to reach room temperature.

Assemble Additional Supplies

- Assemble additional supplies you will need for your injection. These include an alcohol swab, a cotton ball or gauze, and a sharps container

Check the Liquid in the SmartJect® Autoinjector

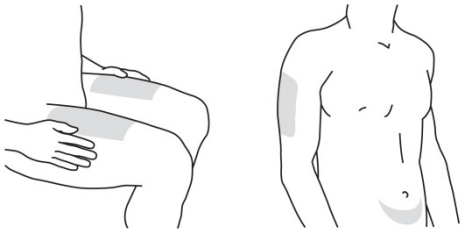
- Look through the viewing window to make sure that the liquid in the autoinjector is clear to slightly opalescent and colourless to slightly yellow
- You may also notice an air bubble – this is normal

DO NOT use if the liquid is discoloured, cloudy or contains particles. If this is the case, please contact your doctor or pharmacist or call 1-800-567-3331 (Canada only) for assistance.

STEP 2: CHOOSING AND PREPARING THE INJECTION SITE

Choose the Injection Site

- The recommended injection site is the front of the middle thighs
- You can also use the lower abdomen below the belly button, except for the two-inch area directly underneath the belly button
- If a caregiver is giving you the injection, the caregiver can also use the outer area of the upper arms
- Injection sites should be rotated. At the time of dosing, if multiple injections are required, the injections should be administered at different sites on the body.



DO NOT inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

Preparing Injection Site

- Thoroughly wash your hands with soap and warm water
- Wipe the injection site with an alcohol swab

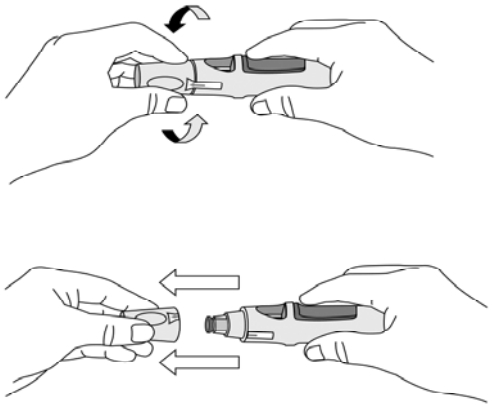
DO NOT touch this area again before giving the injection. Allow the skin to dry before injecting.
DO NOT fan or blow on the clean area.

STEP 3: INJECTING SIMPONI® USING THE SINGLE-USE SmartJect® AUTOINJECTOR

Remove the Cap

The cap should **NOT** be removed until you are ready to inject the medication. The medication should be injected within 5 minutes after the cap has been removed.

- When you are ready to inject, twist the cap slightly to break the security seal
- Pull the cap off and immediately place the cap into the trash

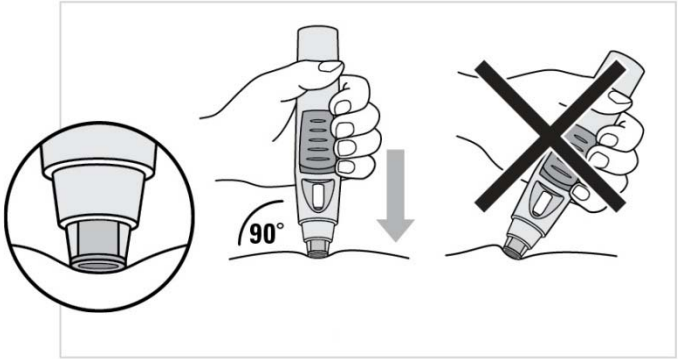


DO NOT put the cap back on because it may damage the needle inside the autoinjector.
Note: Do not use the autoinjector if it is dropped without the cap in place. If you drop the autoinjector without the cap in place, please contact your doctor, pharmacist or call 1-800-567-3331

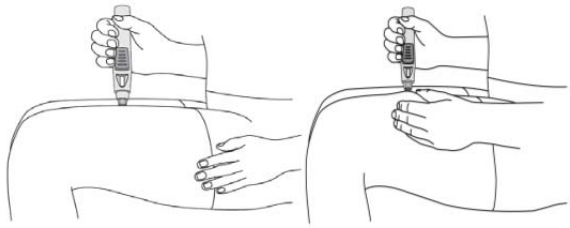
(Canada only) for assistance.

Push the SmartJect® Autoinjector Against the Skin

- Hold the autoinjector comfortably in your hand. **DO NOT** press the button at this time.
- Push the open end of the autoinjector firmly against the skin at a 90-degree angle so that the Safety Sleeve slides up into the clear cover.
- **DO NOT** press the button until **after** the autoinjector is pushed firmly against the skin and the Safety Sleeve slides fully into the Clear Cover.

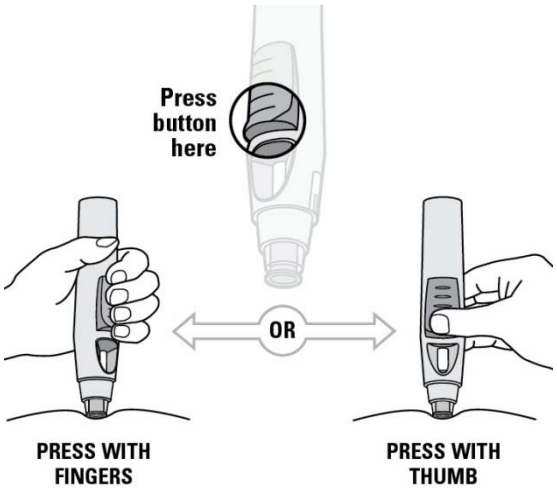


- Injecting without pinching the skin is recommended (left figure). However, if you prefer, you may pinch the skin to create a firmer surface for your injection (right figure).



Press Button to Inject

- **Continue to hold the autoinjector firmly against the skin, and press the front raised part of the button with your fingers or thumb.** You will not be able to press in the button unless the autoinjector is pushed firmly against your skin and the Safety Sleeve slides into the Clear Cover.
- Once the button is pressed, it will remain pressed in so you do not need to keep pressure on it.



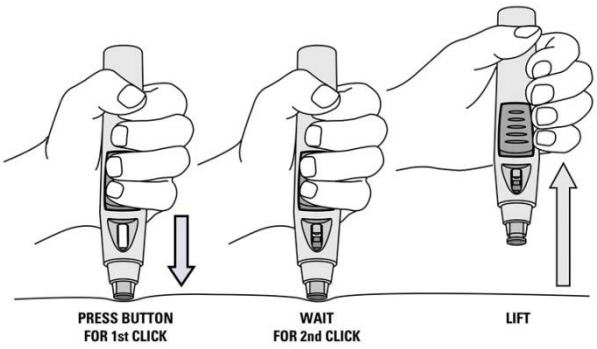
- **You will hear a loud 'click' sound – don't be alarmed**. The first loud "click" indicates that the needle has been inserted and the injection has started. You may or may not feel a needle prick at this time.

DO NOT lift the autoinjector away from your skin. If you pull the autoinjector away from the skin, you may not get your full dose of medicine.

Wait for Second "Click"

- **Continue to hold the autoinjector against the skin until you hear the second "click" (it usually takes about 3–6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound)**
- The second click indicates that the injection is finished and the needle has retracted into the autoinjector
- Lift the autoinjector from the injection site

Note: If you have hearing impairment, count 15 seconds from the time you press the button and then lift the autoinjector from the injection site.

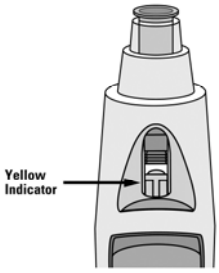


STEP 4: AFTER THE INJECTION

Check the Viewing Window

- After injecting, check the viewing window to make sure that the yellow indicator is visible
- This indicates that the autoinjector has worked properly

- The yellow indicator may not fill the entire viewing window. This is normal.
- If you do not think you received your injection, check the yellow indicator again to confirm that the dose was delivered
- If the yellow indicator is not visible in the viewing window, call 1-800-567-3331 (Canada only) for assistance. DO NOT administer a second dose without speaking to your doctor.



Disposing of the SmartJect® Autoinjector

- Immediately dispose of the autoinjector in the sharps container
- Dispose of the sharps container according to your local regulations

Use Cotton Ball or Gauze

- There may be a small amount of blood or liquid at the injection site, which is normal
- You can press a cotton ball or gauze over the injection site for 10 seconds

DO NOT rub the injection site.

- You may cover the injection site with a small adhesive bandage, if necessary

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common side effects with SIMPONI® include flu, bronchitis, infection of soft tissues, sore throat, upper respiratory infection, sinus infection, runny nose, cold sores, abnormal liver tests, dizziness, numbness or tingling, high blood pressure, fever, hair loss, and redness at the site of injection.

Any medicine may have side effects. These are not all of the side effects with SIMPONI®. Tell your doctor about any side effect that bothers you or does not go away. Ask your doctor or pharmacist for more information (see *WARNINGS AND PRECAUTIONS*).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Serious infections: fever, chills, headache, flu-like symptoms, feel tired, have a cough, blood in your sputum, shortness of breath, night sweats, weight loss, nausea, vomiting, diarrhea, frequency or burning while passing urine, redness or swelling of skin or joint, cold sores, tooth pain or new or worsening of pain in any location while or after receiving SIMPONI®		√	√
Uncommon	Allergic reactions: hives, rash, difficulty breathing, chest pain, high or low blood pressure		√	
	Injection site reactions: rash, swelling, bruising, hives, pain, numbness, and irritation		√	
	Neurological events: changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body		√	
	Appendicitis		√	

HOW TO STORE IT

If you are using SIMPONI® at home, it is important that it is stored in your refrigerator at 2–8 ºC (36–46ºF) although not in the freezer compartment. SIMPONI® should not be frozen. Keep the product in the original carton to protect from light until the time of use. Do not shake.

When needed, for example when you are travelling, SIMPONI® may also be stored at room temperature up to a maximum of 25°C (77 ºF) for a single period up to 30 days in the original carton. Be sure to protect from light until time of use. Once removed from the refrigerator for room temperature storage, it should not be refrigerated again. SIMPONI® should be discarded if not used within 30 days after removal from the refrigerator. It is recommended that you record the room temperature expiration date on the carton after which date SIMPONI® should be discarded.

Always keep medicine out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

• Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting
• Call toll-free at 1-866-234-2345
• Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at:1-800-567-3331 or 1-800-387-8781.

Information about the BioAdvance® Network can be obtained by contacting Janssen Inc. Medical Information at 1-800-567-3331.

This leaflet was prepared by Janssen Inc., Toronto, Ontario M3C 1L9

Last revised:

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PART III: CONSUMER INFORMATION

SIMPONI®
pronounced sim poe NEE
golimumab injection
Single-use Pre-filled Syringe

This leaflet is part III of a three-part "Product Monograph" published when SIMPONI® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SIMPONI®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the Medication is Used For:
SIMPONI® is a prescription medicine that is approved for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, and ulcerative colitis. In these diseases, the body produces too much of a substance called tumor necrosis factor alpha (TNF-alpha). Too much of this substance causes your body's immune system to attack healthy tissue and results in inflammation. Blocking TNF-alpha with SIMPONI® can reduce inflammation associated with these diseases, but can also reduce your immune system's ability to fight off infections.

Rheumatoid Arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis, you will be given SIMPONI®, which you will take in combination with methotrexate. In patients with rheumatoid arthritis, SIMPONI® may help reduce signs and symptoms of inflammatory arthritis (such as pain), may help improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), and may help prevent damage to your bones and joints.

Psoriatic Arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis, you will be given SIMPONI® alone or in combination with methotrexate. In patients with psoriatic arthritis, SIMPONI® may help reduce signs and symptoms of inflammatory arthritis (such as pain), may help improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), and may help to prevent damage to your bones and joints.

Ankylosing Spondylitis
Ankylosing spondylitis is an inflammatory disease of the spine. If you have active ankylosing spondylitis, you will be given SIMPONI® to reduce the signs and symptoms of your disease.

Non-radiographic axial spondyloarthritis
Non-radiographic axial spondyloarthritis is an inflammatory disease of the spine. If you have severe, active non-radiographic axial spondyloarthritis, you will be given SIMPONI® to reduce the signs and symptoms of your disease.

Ulcerative Colitis
Ulcerative colitis (UC) is a chronic inflammatory bowel disorder. In patients with ulcerative colitis, SIMPONI® may

- Reduce the signs and symptoms of your disease
- Induce remission of your disease
- Induce intestinal healing
- Improve your quality of life by helping you feel better
- Maintain control of signs and symptoms of your disease
- Achieve long term remission of your disease

What it Does:
SIMPONI® is a medicine that affects your immune system. SIMPONI® can lower the ability of your immune system to fight infections. Some patients have had serious infections while receiving SIMPONI®, including tuberculosis, and systemic bacterial, and fungal, infections. Some patients have died from these serious infections.

When it Should Not Be Used:
SIMPONI® is a clear to slightly clear, colourless to light yellow solution. This appearance is not unusual for solutions containing protein.

SIMPONI® should not be used:
- after the expiration date on the label
- if the product is damaged
- if the liquid is discoloured, cloudy or you can see other particulate matter floating in it
- if you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated)

SIMPONI® should not be used if you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.

SIMPONI® should not be used if you have heart failure that is moderate or severe.

SIMPONI® should not be used by patients who are allergic to golimumab, latex or any other ingredient (polysorbate 80 or sorbitol) in the formulation or component of the container.

What the Medicinal Ingredient Is:
Golimumab

What the Important Nonmedicinal Ingredients Are:
L-histidine
L-histidine hydrochloride
Polysorbate 80
Sorbitol
Water for injection

No preservatives are present.

What Dosage Forms it Comes In:
SIMPONI® is available as a single-use autoinjector and as a single-use pre-filled syringe.
Each single-use autoinjector contains either 50 mg golimumab per

0.5 mL, or 100 mg golimumab per 1 mL.
Each single-use pre-filled syringe contains either 50 mg golimumab per 0.5 mL, or 100 mg golimumab per 1 mL.

Where I May Receive Training on How to Self-Inject SIMPONI®:
The BioAdvance® Network has been established to offer training on how to self-inject SIMPONI®. Patients can be trained by BioAdvance® qualified healthcare professionals either at their home or at BioAdvance® clinics located across Canada. Contact your doctor if you have any questions.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal and bacterial infections), have been reported in patients receiving SIMPONI® and other similar medicines. Some patients with these infections have died. Prior to treatment with SIMPONI®, you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by a fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or travelled. If you develop an infection during treatment with SIMPONI®, you should tell your doctor right away.

Prior to treatment with SIMPONI®, you should tell your doctor if you have had tuberculosis or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with SIMPONI®.

Treatment with SIMPONI® must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking SIMPONI® and for 6 months after you receive the medicine. If you need surgery, tell your doctor that you have taken SIMPONI®.

Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF blockers, of which SIMPONI® is a member.

BEFORE you use SIMPONI® talk to your doctor or pharmacist if you:

- have any kind of infection even if it is very minor
- have an infection that won't go away or a history of infection that keeps coming back
- have had TB (tuberculosis), or have recently been near anyone who might have TB. Your doctor will evaluate you for TB and perform a skin or blood test. If your doctor feels that you are at risk for TB, he or she may start treating you for TB before you begin SIMPONI® therapy
- have or have had a hepatitis B infection
- have heart failure, or if you previously had or currently have any heart condition. If you develop new or worsening symptoms of heart failure, such as shortness of breath or swelling of your feet, you must notify your doctor
- have or have had a condition that affects your nervous system, like multiple sclerosis or Guillain-Barré syndrome. You should tell your doctor if you experience weakness in your arms or legs, numbness, tingling, or visual disturbances.
- have or have had any type of cancer
- have recently received or are scheduled to receive a vaccine.
- have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- have a latex allergy
- are pregnant, planning to become pregnant, or breastfeeding. SIMPONI® should only be used during pregnancy if clearly needed. If you are being treated with SIMPONI®, you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last SIMPONI® injection. Women who are breastfeeding should talk to their doctor about whether or not to use SIMPONI®.
- received SIMPONI® while you were pregnant as your baby may be at higher risk of getting an infection. It is important to tell your baby's doctor and other health professionals about your SIMPONI® use before the baby receives any vaccine as certain vaccines may put your baby at higher risk of infections

What Are The Possible Side Effects With SIMPONI®?
Serious side effects that may require treatment can occur during SIMPONI® therapy. Possible serious side effects of SIMPONI® include:

Serious Infections
(See What it Does). If you develop a fever, chills, headache, flu-like symptoms, feel tired, have a cough, blood in your sputum, shortness of breath, night sweats, weight loss, nausea, vomiting, diarrhea, frequency or burning while passing urine, redness or swelling of skin or joint, cold sores, tooth pain or new or worsening of pain in any location while or after receiving SIMPONI®, you should tell your doctor right away because these could be signs that you are getting an infection.

Treatment with TNF-blocking agents such as SIMPONI® may result in reactivation of the hepatitis B virus in patients who carry this virus. If you know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with SIMPONI®. Your doctor should do a blood test for hepatitis B virus before you start treatment with SIMPONI®.

Allergic Reactions
Some patients may get allergic reactions to SIMPONI®. Some

reactions may be serious, and in rare instances, life-threatening. Some of these reactions occurred after the first administration of SIMPONI®. Symptoms of an allergic reaction may include hives, rash, difficulty breathing, chest pain, and high or low blood pressure. You should contact your doctor if you experience any of these symptoms.

Needle Cover with Dry Natural Rubber (a form of latex)
The needle cover on the pre-filled syringe and the autoinjector contains dry natural rubber (a form of latex). This may cause allergic reactions in people who are sensitive to latex. Tell your doctor if you have ever had an allergic reaction to latex or developed any allergic reaction to SIMPONI® injection.

Injection Site Reactions
Some patients develop reactions at the injection site at their skin after SIMPONI® injections. These reactions may include mild rash, swelling, bruising, hives, pain, numbness, and irritation. You should contact your doctor if you experience severe symptoms at injection site.

Cancer
In clinical studies, reports of blood cancer called lymphoma were more frequent in patients on SIMPONI® than expected for people in general. People who have been treated for rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis for a long time, particularly those with highly active disease may be more prone to develop lymphoma. Cancers, other than lymphoma, have also been reported in patients treated with SIMPONI® or other TNF-blockers. In a study of SIMPONI® in patients with severe, persistent asthma, cancers occurred in SIMPONI®-treated patients but not in control treated patients. If you have severe, persistent asthma you should discuss with your doctor whether SIMPONI® is appropriate for you. Some patients treated with SIMPONI® have developed certain kinds of skin cancer like melanoma. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.

Rarely, a specific and severe type of lymphoma called Hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers, of which SIMPONI® is a member. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and had also received drugs known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking IMURAN (azathioprine) or PURINETHOL (6-mercaptopurine) with SIMPONI®.

You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking SIMPONI®. Whether you decide to use SIMPONI® or not, you should discuss with your doctor the cancer screening measures and impact of lifestyle choices on the risk of developing cancer.

Congestive Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blocking agents, including SIMPONI®. Some of these patients died. SIMPONI® has not been studied in patients with CHF. Tell your doctor if you have heart failure. If you have mild heart failure and your doctor decides to administer SIMPONI®, your condition should be closely monitored during treatment. If you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet), you should contact your doctor right away.

Neurological Events
In rare instances patients treated with TNF-blocking agents may develop diseases such as multiple sclerosis or Guillain-Barré syndrome. Tell your doctor if you have a history of a neurological disease. If you develop symptoms of neurological disease such as changes in your vision, weakness in your arms or legs, or numbness or tingling in any part of your body, you should contact your doctor right away.

Blood Problems
In some instances, patients treated with TNF-blocking agents may develop low blood counts. If you develop symptoms such as persistent fever, bleeding, or bruising, you should contact your doctor right away.

Vaccinations
You should not receive certain vaccines while using SIMPONI®. If you have recently received or are scheduled to receive a vaccine, please inform your doctor.

Certain vaccinations may cause infections. If you received SIMPONI® while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important to tell your baby's doctor and other health care professionals about your SIMPONI® use so they can decide when your baby should receive any vaccine.

Liver Problems
There have been cases where patients taking SIMPONI® developed liver problems. Signs that you could be having a problem include: skin and eyes turning yellow, dark brown-coloured urine, right-sided abdominal pain, fever, nausea, vomiting, and severe fatigue. You should contact your doctor right away if you experience these symptoms.

Driving and Using Machines
SIMPONI® may have a minor influence on your ability to drive and use machines. Dizziness may occur following administration of SIMPONI®. If this happens, do not drive or use any tools or machines.

Check the Prescribed Strength
SIMPONI® is available in 50 mg and 100 mg strengths. When you receive your SIMPONI® make sure the strength matches what was prescribed to you by your doctor for your condition. Contact

your doctor if you are not sure if you have received the correct strength.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take. These include any other medicines to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis.

Drugs that may interact with SIMPONI® include: prescription and non-prescription medicines, vitamins, and herbal supplements.

Tell your doctor if you take KINERET (anakinra) or ORENCIA (abatacept) or other immunosuppressant medications. SIMPONI® should not be taken together with anakinra or abatacept. Also, tell your doctor if you are taking other medications that affect your immune system.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine.

PROPER USE OF THIS MEDICATION

- For rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis SIMPONI® 50 mg is given by injection under the skin (subcutaneously) with an autoinjector or a pre-filled syringe once a month, on the same date each month.
- If you are receiving SIMPONI® for ulcerative colitis, all injections will be given subcutaneously. You will receive your first 200 mg dose followed by an additional 100 mg dose 2 weeks after the first dose. You will receive a 50 mg or 100 mg dose every 4 weeks thereafter as directed by your doctor.
- SIMPONI® is intended for use under the guidance and supervision of your doctor. Your doctor will tell you how often to take SIMPONI®. **Do not take SIMPONI® more often than prescribed**. If your doctor determines that it is appropriate, you may be able to administer SIMPONI® to yourself, after proper training in injection technique (**see** *INSTRUCTIONS FOR INJECTING SIMPONI® USING A PRE-FILLED SYRINGE*).
- If you take more SIMPONI® than you were told to take, call your doctor.
- Do not miss any doses of SIMPONI®. (See *Missed Dose*).

Usual Dose:
Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Non-radiographic axial spondyloarthritis
50 mg of SIMPONI® given as a subcutaneous injection once a month, on the same date each month.

Ulcerative Colitis
200 mg of SIMPONI® given as a subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 50 mg or 100 mg every 4 weeks, thereafter. Your doctor may consider doing a blood test (therapeutic drug monitoring) to determine how much golimumab is in your blood stream in order to optimize your dose of SIMPONI®.

Overdose:
Single doses up to 10 mg/kg intravenously have been administered in a clinical study without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

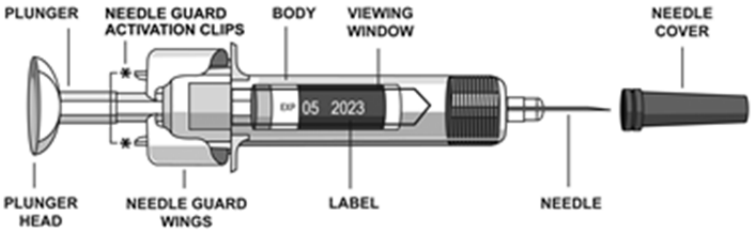
Missed Dose:
Patients who miss a dose of SIMPONI®, should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.
If you are not sure what to do, talk to your doctor or pharmacist.

INSTRUCTIONS FOR INJECTING SIMPONI® USING A PRE-FILLED SYRINGE

If you would like to self-inject SIMPONI®, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your healthcare professional to schedule a training session.

STEP 1: PREPARING TO USE THE PRE-FILLED SYRINGE

The diagram below shows what the pre-filled syringe looks like:

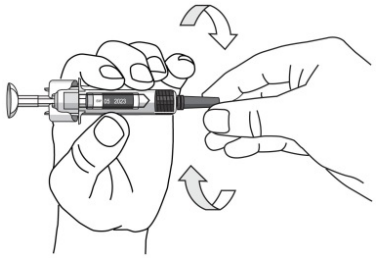


Hold the pre-filled syringe by the body of the syringe.

DO NOT hold the pre-filled syringe by the plunger head, plunger, needle guard wings, or needle cover.
DO NOT pull back on the plunger at any time.
DO NOT shake the pre-filled syringe at any time.
DO NOT remove the needle cover from the pre-filled syringe until instructed to do so.
DO NOT touch the needle guard activation clips (as indicated by asterisks [*] in the first illustration) to prevent prematurely covering the needle with the needle guard.

Check the Expiration Date

- Check the expiration date (as indicated by "EXP") on the label by looking through the viewing window located within the body of the pre-filled syringe
- If you cannot see the expiration date through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the expiration date to the viewing window
- You can also check the expiration date printed on the carton
- If the expiration date has passed, or if the pre-filled syringe has been kept at room temperature 25ºC (77ºF) for longer than 30 days or if the pre-filled syringe has been stored above 25ºC (77ºF) **DO NOT** use the pre-filled syringe. Please contact your doctor or pharmacist or call 1-800-567-3331 (Canada only) for assistance.



Wait 30 Minutes

- To ensure proper injection, allow the pre-filled syringe to sit at room temperature outside of the carton for 30 minutes out of the reach of children

DO NOT warm the pre-filled syringe in any other way. (For example, **DO NOT** warm it in a microwave or in hot water.)
DO NOT remove the pre-filled syringe needle cover while allowing it to reach room temperature.

Assemble Additional Supplies

- Assemble additional supplies you will need for your injection. These include an alcohol swab, a cotton ball or gauze, and a sharps container for syringe disposal

Check the Liquid in the Pre-filled Syringe

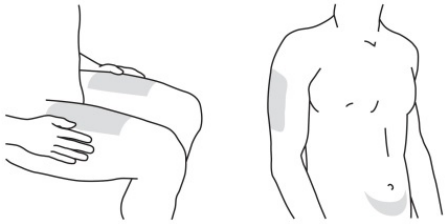
- Hold the pre-filled syringe by its body with the covered needle pointing downward
- Look at the liquid through the viewing window of the pre-filled syringe to make sure that it is clear to slightly opalescent and colourless to slightly yellow
- If you cannot see the liquid through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the liquid to the viewing window
- You may also notice an air bubble – this is normal

DO NOT use if the liquid is discoloured, cloudy or contains particles. If this is the case, please contact your doctor or pharmacist or call 1-800-567-3331 (Canada only) for assistance.

STEP 2: CHOOSING AND PREPARING THE INJECTION SITE

Choose the Injection Site

- The recommended injection site is the front of the middle thighs
- You can also use the lower abdomen below the belly button, except for the two-inch area directly underneath the belly button
- If a caregiver is giving you the injection, the caregiver can also use the outer area of the upper arms
- Injection sites should be rotated. At the time of dosing, if multiple injections are required, the injections should be administered at different sites on the body.



DO NOT inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

Preparing the Injection Site

- Thoroughly wash your hands with soap and warm water
- Wipe the injection site with an alcohol swab

DO NOT touch this area again before giving the injection. Allow the skin to dry before injecting.
DO NOT fan or blow on the clean area.

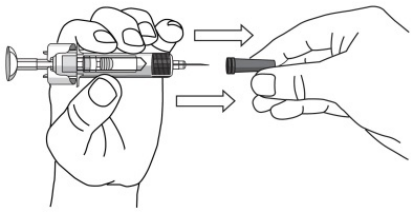
STEP 3: INJECTING THE MEDICATION

The needle cover should NOT be removed until you are ready to inject the medication. The medication should be injected within 5 minutes after the needle cover has been removed.

Remove the Needle Cover

DO NOT touch the plunger during needle cover removal.

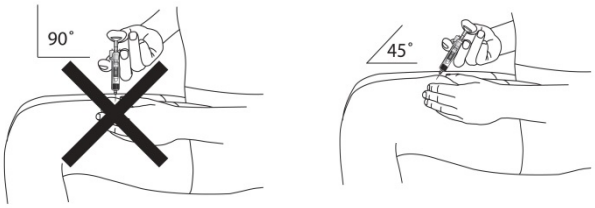
- When you are ready to inject, hold the body of the pre-filled syringe with one hand, and pull the needle cover straight off
- Place the needle cover into the trash
- You may notice an air bubble in the pre-filled syringe. You **DO NOT** need to remove the air bubble
- You may also see a drop of liquid at the end of the needle – this is normal



DO NOT touch the needle or allow it to touch any surface.
DO NOT use the pre-filled syringe if it is dropped without the needle cover in place. If you drop the pre-filled syringe without the needle cover in place, please contact your doctor, pharmacist or call 1-800-567-3331 (Canada only) for assistance.

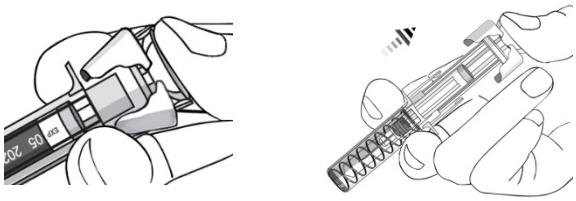
Position the Syringe and Inject the Medication

- Hold the body of the pre-filled syringe in one hand between the middle and index fingers and place the thumb on top of the plunger head



DO NOT pull back on the plunger at any time

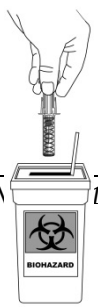
- Use the other hand to gently pinch the area of skin that you previously cleaned. Hold firmly
- Place the needle at approximately a 45-degree angle to the pinched skin. In a single and swift motion, insert the needle through the skin as far as it will go
- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings
- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin
- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard as shown by the illustration



STEP 4: AFTER THE INJECTION

Disposing of the Empty Syringe

- Immediately dispose of the empty syringe into the sharps container. For your safety and health and for the safety of others, needles and empty syringes **must NEVER** be re-used
- Dispose of the sharps container according to your local regulations



Use Cotton Ball or Gauze

- There may be a small amount of blood or liquid at the injection site, which is normal
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds

DO NOT rub the injection site.

- You may cover the injection site with a small adhesive bandage, if necessary

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common side effects with SIMPONI® include flu, bronchitis, infection of soft tissues, sore throat, upper respiratory infection, sinus infection, runny nose, cold sores, abnormal liver tests, dizziness, numbness or tingling, high blood pressure, fever, hair loss and redness at the site of injection.

Any medicine may have side effects. These are not all of the side effects with SIMPONI®. Tell your doctor about any side effect that bothers you or does not go away. Ask your doctor or pharmacist for more information. (See *WARNINGS AND PRECAUTIONS*).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Serious infections: fever, chills, headache, flu-like symptoms, feel tired, have a cough, blood in your sputum, shortness of breath, night sweats, weight loss, nausea, vomiting, diarrhea, frequency or burning while passing urine, redness or swelling of skin or joint, cold sores, tooth pain or new or worsening of pain in any location while or after receiving SIMPONI®		√	√
Uncommon	Allergic reactions: hives, rash, difficulty breathing, chest pain, high or low blood pressure		√	
	Injection site reactions: rash, swelling, bruising, hives, pain, numbness, and irritation		√	
	Neurological events: changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body		√	
	Appendicitis		√	

HOW TO STORE IT

If you are using SIMPONI® at home, it is important that it is stored in your refrigerator at 2–8 ºC (36–46ºF) although not in the freezer compartment. SIMPONI® should not be frozen. Keep the product in the original carton to protect from light until the time of use. Do not shake.

When needed, for example when you are travelling, SIMPONI® may also be stored at room temperature up to a maximum of 25°C (77 ºF) for a single period up to 30 days in the original carton. Be sure to protect from light until time of use. Once removed from the refrigerator for room temperature storage, it should not be refrigerated again. SIMPONI® should be discarded if not used within 30 days after removal from the refrigerator. It is recommended that you record the room temperature expiration date on the carton after which date SIMPONI® should be discarded.

Always keep medicine out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

• Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting
• Call toll-free at 1-866-234-2345
• Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.
Information about the BioAdvance® Network can be obtained by contacting Janssen Inc. at: 1-800-567-3331.

This leaflet was prepared by Janssen Inc., Toronto,
Ontario M3C 1L9

Last revised:

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PART III: CONSUMER INFORMATION

SIMPONI® I.V.
pronounced sim poe NEE
golimumab for injection
Single-use Vial

This leaflet is part III of a three-part "Product Monograph" published when SIMPONI® I.V. was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SIMPONI® I.V. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the Medication Is Used For:
SIMPONI® I.V. is a prescription medicine that is approved for the treatment of adult patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. In these diseases, the body produces too much of a substance called tumour necrosis factor alpha (TNF-alpha). Too much of this substance causes your body's immune system to attack healthy tissue and results in inflammation. Blocking TNF-alpha with SIMPONI® I.V. can reduce inflammation associated with this disease, but can also reduce your immune system's ability to fight off infections.

Rheumatoid Arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis, you will be given SIMPONI® I.V., which you will take in combination with methotrexate. In patients with rheumatoid arthritis, SIMPONI® I.V. may help reduce signs and symptoms of inflammatory arthritis (such as pain).

Psoriatic Arthritis
SIMPONI® I.V. is a prescription medicine that is approved for adults with active psoriatic arthritis.

Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis that has not responded to other medications and you are an adult, you may be given SIMPONI® I.V., alone or in combination with methotrexate, to help reduce signs and symptoms of inflammatory arthritis (such as pain), improve your ability to do simple daily activities (such as dressing, walking and climbing stairs), prevent damage to your bones and joints and improve your psoriasis.

Ankylosing Spondylitis
SIMPONI® I.V. is a prescription medicine that is approved for adults with ankylosing spondylitis.

Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis that has not responded to other medications and you are an adult, you may be given SIMPONI® I.V. to reduce the signs and symptoms of your disease and improve your ability to do simple daily activities (such as dressing, walking and climbing stairs).

What It Does:
SIMPONI® I.V. is a medicine that affects your immune system. SIMPONI® I.V. can lower the ability of your immune system to fight infections. Some patients have had serious infections while receiving SIMPONI® I.V., including tuberculosis, and systemic bacterial, and fungal, infections. Some patients have died from these serious infections.

When It Should Not Be Used:
SIMPONI® I.V. is a clear, colourless to light yellow solution. This appearance is not unusual for solutions containing protein.
SIMPONI® I.V. should not be used:

- after the expiration date on the label
- if the product is damaged
- if the liquid is discoloured, cloudy or you can see other particulate matter floating in it
- if you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated)

SIMPONI® I.V. should not be used if you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.

SIMPONI® I.V. should not be used if you have heart failure that is moderate or severe.

SIMPONI® I.V. should not be used by patients who are allergic to golimumab or any other ingredient (polysorbate 80 or sorbitol) in the formulation.

What the Medicinal Ingredient Is:
Golimumab

What the Important Nonmedicinal Ingredients Are:
L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Sorbitol
Water for injection

No preservatives are present.

What Dosage Forms It Comes In:
SIMPONI® I.V. is available as a sterile solution in single-use vials.
Each vial contains 50 mg golimumab in 4.0 mL.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal and bacterial infections), have been reported in patients receiving SIMPONI® I.V. and other

similar medicines. Some patients with these infections have died. Prior to treatment with SIMPONI® I.V., you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by a fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or travelled. If you develop an infection during treatment with SIMPONI® I.V., you should tell your doctor right away.

Prior to treatment with SIMPONI® I.V., you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with SIMPONI® I.V.

Treatment with SIMPONI® I.V. must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking SIMPONI® I.V. and for 6 months after you receive the medicine. If you need surgery, tell your doctor that you have taken SIMPONI® I.V.

Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF blockers, of which SIMPONI® I.V. is a member.

BEFORE you use SIMPONI® I.V. talk to your doctor or pharmacist if you:

- have any kind of infection even if it is very minor
- have an infection that won't go away or a history of infection that keeps coming back
- have had tuberculosis, or have recently been near anyone who might have tuberculosis. Your doctor will evaluate you for tuberculosis and perform a skin or a blood test. If your doctor feels that you are at risk for tuberculosis, he or she may start treating you for tuberculosis before you begin SIMPONI® I.V. therapy
- have or have had a hepatitis B infection
- have heart failure, or if you previously had or currently have any heart condition. If you develop new or worsening symptoms of heart failure, such as shortness of breath or swelling of your feet, you must notify your doctor
- have or have had a condition that affects your nervous system, like multiple sclerosis or Guillain-Barré syndrome. You should tell your doctor if you experience weakness in your arms or legs, numbness, tingling, or visual disturbances
- have or have had any type of cancer
- have recently received or are scheduled to receive a vaccine
- have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- are pregnant, planning to become pregnant, or breastfeeding. SIMPONI® I.V. should only be used during pregnancy if clearly needed. If you are being treated with SIMPONI® I.V., you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last SIMPONI® I.V. infusion. Women who are breastfeeding should talk to their doctor about whether or not to use SIMPONI® I.V.
- received SIMPONI® I.V. while you were pregnant as your baby may be at higher risk of getting an infection. It is important to tell your baby's doctor and other health professionals about your SIMPONI® I.V. use before the baby receives any vaccine as certain vaccines may put your baby at higher risk of infections

What Are the Possible Side Effects with SIMPONI® I.V.?

Serious side effects that may require treatment can occur during SIMPONI® I.V. therapy. Possible serious side effects of SIMPONI® I.V. include:

Serious Infections

(See What It Does) If you develop a fever, chills, headache, flu-like symptoms, feel tired, have a cough, blood in your sputum, shortness of breath, night sweats, weight loss, nausea, vomiting, diarrhea, frequency or burning while passing urine, redness or swelling of skin or joint, cold sores, tooth pain or new or worsening of pain in any location while or after receiving SIMPONI® I.V., you should tell your doctor right away because these could be signs that you are getting an infection.

Treatment with TNF-blocking agents such as SIMPONI® I.V. may result in reactivation of the hepatitis B virus in patients who carry this virus. If you know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with SIMPONI® I.V. Your doctor should do a blood test for hepatitis B virus before you start treatment with SIMPONI® I.V.

Allergic Reactions

Some patients may get allergic reactions to SIMPONI® I.V. Some reactions may be serious, and in rare instances, life-threatening. Some of these reactions occurred after the first administration of SIMPONI® I.V. Symptoms of an allergic reaction may include hives, rash, difficulty breathing, chest pain, and high or low blood pressure. You should contact your doctor if you experience any of these symptoms. If an allergic reaction occurs while getting a SIMPONI® I.V. infusion or shortly afterwards, your doctor may decide to stop your SIMPONI® I.V. infusion and/or give you medication to treat the reaction.

Cancer

In clinical studies, reports of a blood cancer called lymphoma were more frequent in patients on SIMPONI® administered

subcutaneously than expected for people in general. People who have been treated for rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis for a long time, particularly those with highly active disease may be more prone to develop lymphoma. Cancers, other than lymphoma, have also been reported in patients treated with SIMPONI® I.V. or other TNF-blockers. In a study of SIMPONI® administered subcutaneously in patients with severe, persistent asthma, cancers occurred in SIMPONI®-treated patients but not in control-treated patients. If you have severe, persistent asthma, you should discuss with your doctor whether SIMPONI® I.V. is appropriate for you. Some patients treated with SIMPONI® I.V. have developed certain kinds of skin cancer like melanoma. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of developing lymphoma or other cancers may increase.

Rarely, a specific and severe type of lymphoma called hepatosplenic T-cell lymphoma has been observed in patients taking other TNF-blockers, of which SIMPONI® I.V. is a member. Most of these patients were adolescent or young adult males. This type of cancer has usually resulted in death. Almost all of these patients were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and had also received drugs known as azathioprine or 6-mercaptopurine. Tell your doctor if you are taking IMURAN (azathioprine) or PURINETHOL (6-mercaptopurine) with SIMPONI® I.V.

You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking SIMPONI® I.V. Whether you decide to use SIMPONI® I.V. or not, you should discuss with your doctor the cancer screening measures and impact of lifestyle choices on the risk of developing cancer.

Congestive Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blocking agents, including SIMPONI® I.V. Some of these patients died. SIMPONI® I.V. has not been studied in patients with CHF. Tell your doctor if you have heart failure. If you have mild heart failure and your doctor decides to administer SIMPONI® I.V., your condition should be closely monitored during treatment. If you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet), you should contact your doctor right away.

Neurological Events
In rare instances patients treated with TNF-blocking agents may develop diseases such as multiple sclerosis or Guillain-Barré syndrome. Tell your doctor if you have a history of a neurological disease. If you develop symptoms of neurological disease such as changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body, you should contact your doctor right away.

Blood Problems
In some instances, patients treated with TNF-blocking agents may develop low blood counts. Low blood counts have been seen with SIMPONI® I.V. If you develop symptoms such as persistent fever, bleeding, or bruising, you should contact your doctor right away.

Vaccinations
You should not receive certain vaccines while using SIMPONI® I.V. If you have recently received or are scheduled to receive a vaccine, please inform your doctor.

Certain vaccinations may cause infections. If you received SIMPONI® I.V. while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important to tell your baby's doctor and other health care professionals about your SIMPONI® I.V. use so they can decide when your baby should receive any vaccine.

Liver Problems
There have been cases where patients taking SIMPONI® I.V. developed liver problems. Signs that you could be having a problem include: skin and eyes turning yellow, dark brown-coloured urine, right-sided abdominal pain, fever, nausea, vomiting, and severe fatigue. You should contact your doctor right away if you experience these symptoms.

Driving and Using Machines
SIMPONI® I.V. may have a minor influence on your ability to drive and use machines. Dizziness may occur following administration of SIMPONI® I.V. If this happens, do not drive or use any tools or machines.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take. These include any other medicines to treat rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.

Drugs that may interact with SIMPONI® I.V. include: prescription and non-prescription medicines, vitamins, and herbal supplements.

Tell your doctor if you take KINERET (anakinra) or ORENCIA (abatacept) or other immunosuppressant medications. SIMPONI® I.V. should not be taken together with anakinra or abatacept. Also, tell your doctor if you are taking other medications that affect your immune system.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine.

PROPER USE OF THIS MEDICATION

- SIMPONI® I.V. will be given to you by a doctor or nurse. The doctor or nurse will prepare the SIMPONI® I.V. solution for intravenous infusion.
- The SIMPONI® I.V. solution will be given through a needle placed in a vein usually in an arm. The infusion will take approximately 30 minutes.

Usual Dose:
Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis

- Your doctor will decide your dose (in mg) based on your weight. The dose is 2 mg for every kg of body weight. The table below shows how often you will usually have this medicine.

1st treatment	Initial treatment
2nd treatment	4 weeks after your 1st treatment
Further treatments	Every 8 weeks

Overdose:
Single doses up to 10 mg/kg intravenously have been administered in a clinical study without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget or miss an appointment to receive SIMPONI® I.V., make another appointment as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects with SIMPONI® I.V. include: flu, bronchitis, infection of soft tissues, sore throat, upper respiratory infection, sinus infection, runny nose, cold sores, abnormal liver tests, dizziness, numbness or tingling, high blood pressure, fever, hair loss and redness at the site of injection.

Any medicine may have side effects. These are not all of the side effects with SIMPONI® I.V. Tell your doctor about any side effect that bothers you or does not go away. Ask your doctor or pharmacist for more information.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common (≥1% and <10%)	Serious infections: fever, chills, headache, flu-like symptoms, feel tired, have a cough, blood in your sputum, shortness of breath, night sweats, weight loss, nausea, vomiting, diarrhea, frequency or burning while passing urine, redness or swelling of skin or joint, cold sores, tooth pain or new or worsening of pain in any location while or after receiving SIMPONI® I.V.		√	√
	Infusion reactions: rash, swelling, bruising, hives, pain, numbness, and irritation		√	
Uncommon (≥0.1% and <1%)	Allergic reactions: hives, rash, difficulty breathing, chest pain, high or low blood pressure		√	
	Neurological events: changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body		√	
	Anemia (low red blood cells)		√	
	Appendicitis		√	

HOW TO STORE IT

SIMPONI® I.V. must be stored in the original package in the refrigerator before use. SIMPONI® I.V. should not be frozen. It must be kept out of the reach and sight of children. Keep the

product in the original carton to protect from light until the time of use. Do not shake.

When needed, for example when you are travelling, SIMPONI® I.V. may also be stored at room temperature up to a maximum of 25°C (77 ºF) for a single period up to 30 days in the original carton. Be sure to protect from light until time of use. Once removed from the refrigerator for room temperature storage, it should not be refrigerated again. SIMPONI® I.V. should be discarded if not used within 30 days after removal from the refrigerator. It is recommended that you record the room temperature expiration date on the carton after which date SIMPONI® I.V. should be discarded.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

• Report online at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting• Call toll-free at 1-866-234-2345
• Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions, concerns, or the full Product Monograph go to: www.janssen.com/canada or contact the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario M3C 1L9

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