SIMPONI®

Solution for Injection in a pre-filled syringe
Solution for Injection in a pre-filled pen, SmartJect
NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SIMPONI 50 mg Solution for Injection in a pre-filled syringe

SIMPONI 50 mg Solution for Injection in a pre-filled pen, SmartJect

SIMPONI 100 mg Solution for Injection in a pre-filled syringe

SIMPONI 100 mg Solution for Injection in a pre-filled pen, SmartJect

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL single-use pre-filled syringe or pre-filled pen contains 50 mg of golimumab*.

Each 1.0mL single-use pre-filled syringe or pre-filled pen contains 100mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipient(s) with known effect:

Each pre-filled pen contains 20.5 mg sorbitol per 50 mg dose or 41 mg sorbitol per 100 mg dose.

Each pre-filled syringe contains 20.5 mg sorbitol per 50 mg dose or 41 mg sorbitol per 100 mg dose.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

Solution for injection in pre-filled pen (injection), SmartJect

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)

SIMPONI, in combination with methotrexate (MTX), is indicated for:

- the treatment of active rheumatoid arthritis in adult patients when the response to DMARD therapy has been inadequate.
- the treatment of active rheumatoid arthritis in adult patients not previously treated with MTX.

SIMPONI has also been shown to reduce the rate of progression of joint damage as measured by X-ray, improve physical function and health related quality of life. SIMPONI can be used in patients previously treated with one or more TNF inhibitor(s).

Psoriatic arthritis (PsA)

SIMPONI, alone or in combination with MTX, is indicated for:

The treatment of active psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. SIMPONI has also been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray, improve physical function and health related quality of life.

Ankylosing spondylitis (AS)

SIMPONI is indicated for:

The treatment of active ankylosing spondylitis in adult patients. SIMPONI has also been shown to improve physical function and health related quality of life.

Ulcerative colitis (UC)

SIMPONI is indicated for:

The treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA) or who are intolerant to or have medical contraindications for such therapies.

4.2 Dose and method of administration

SIMPONI treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or ulcerative colitis.

After proper training in SC injection technique, patients may self-inject with SIMPONI if their physician determines that this is appropriate, with medical follow-up as necessary.

Rheumatoid arthritis

SIMPONI 50 mg given as a subcutaneous injection once a month, on the same date each month.

Psoriatic arthritis

SIMPONI 50 mg given as a subcutaneous injection once a month, on the same date each month.

Ankylosing spondylitis

SIMPONI 50 mg given as a subcutaneous injection once a month, on the same date each month.

Ulcerative colitis

SIMPONI 200 mg given as a subcutaneous injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks, thereafter.

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

Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Special populations

Elderly patients (≥ 65 years)

No dosage adjustment is required in the elderly.

Paediatric patients (< 18 years)

SIMPONI is not recommended for use in children below age 18 due to a lack of data on efficacy and safety.

Patients with impaired renal and/or hepatic function

SIMPONI has not been studied in these patient populations. No dose recommendations can be made.

4.3 Contraindications

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see **section 4.4**).
- Concurrent administration of SIMPONI with anakinra or abatacept (see **section 4.4**).
- Moderate or severe heart failure (NYHA class III/IV) (see **section 4.4**).
- Hypersensitivity to the active substance or to any of the excipients (see **section 6.1**).

4.4 Special warnings and precautions for use

Infections

Serious and sometimes fatal infections due to bacterial (including sepsis and pneumonia), mycobacterial, invasive fungal, viral, protozoal or other opportunistic pathogens have been reported in patients receiving TNF blocking agents, including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported with TNF-blockers. Patients have frequently presented with disseminated rather than localised disease, and were often taking concomitant immunosuppressants such as methotrexate (MTX) or corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended (see **sections 4.3** and **4.5**).

Treatment with SIMPONI should not be initiated in patients with an active infection, including clinically important localised infections. The risks and benefits of treatment should be considered prior to initiating or continuing SIMPONI in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided in or travelled to areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. SIMPONI should be discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with SIMPONI should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Invasive Fungal Infections

For SIMPONI-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made 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.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including SIMPONI. In addition, patients who have previously received treatment for latent or active tuberculosis have developed tuberculosis while receiving TNF-blockers, including SIMPONI. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent infection prior to initiating SIMPONI and periodically during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with SIMPONI.

Anti-tuberculosis therapy should be considered prior to initiation of SIMPONI 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, treatment for latent tuberculosis should be considered in patients who have significant risk factors for tuberculosis 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.

Cases of active tuberculosis have occurred in patients treated with SIMPONI during and after treatment for latent tuberculosis. Patients receiving SIMPONI 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 infections. Tuberculosis should be strongly considered in patients who develop a new infection during SIMPONI treatment, especially in patients who have previously or recently travelled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active tuberculosis was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-treated patients and 674 placebo-treated patients, respectively. Cases of tuberculosis included pulmonary and extra pulmonary tuberculosis. The overwhelming majority of the tuberculosis cases occurred in countries with a high incidence rate of tuberculosis.

Hepatitis B virus reactivation

The use of TNF blockers including SIMPONI has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). Patients should be tested for HBV infection before initiating treatment with immunosuppressants, including SIMPONI. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. 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 at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, physicians should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely.

Malignancies

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.

Paediatric Malignancy

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF-blocking agents (initiation of therapy ≤ 18 years of age) to treat Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other conditions. Approximately half the reports were lymphomas (Hodgkin's and non-Hodgkin's lymphoma). The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine or 6-mercaptopurine. The role of TNF blockers in the development of malignancies in children and adolescents remains unclear.

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.

Leukaemia

Cases of acute and chronic leukaemia have been reported with TNF-blocker use, including SIMPONI, 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 2-fold) than the general population for the development of leukaemia.

Malignancies other than lymphoma

In the controlled portions of the SIMPONI Phase 2 and Phase 3 clinical trials in RA, PsA, AS and UC, 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 malignancies were reported in patients treated with SIMPONI compared with control patients (see **section 4.8**). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

Colon Dysplasia/Carcinoma

It is not known if SIMPONI treatment influences the risk of 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, 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 SIMPONI (see **section 4.8**). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including SIMPONI. Some cases had a fatal outcome. Cases of CHF in patients with known cardiovascular risk factors have been observed with SIMPONI. 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 hospitalisation or increased mortality. SIMPONI has not been studied in patients with a history of CHF And SIMPONI should be used with caution in patients with CHF. If a decision is made to administer SIMPONI to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear.

Demyelinating disorders

Use of TNF blocking agents, including SIMPONI, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI should be considered if these disorders develop. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of SIMPONI therapy.

Autoimmunity

Treatment with SIMPONI 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 golimumab, treatment should be discontinued (see **section 4.8 - Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies**).

Haematological cytopaenias

There have been post-marketing reports of pancytopaenia, leukopaenia, neutropaenia, agranulocytosis, aplastic anaemia, and thrombocytopaenia in patients receiving TNF-blockers. Cytopaenias including pancytopaenia, have been infrequently reported with SIMPONI in clinical trials. 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 therapy should be considered in patients with confirmed significant haematological abnormalities.

Concurrent administration of SIMPONI with anakinra

Serious infections and neutropaenia were seen in clinical studies with concurrent use of anakinra and another TNF blocking agent, etanercept, with 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 and anakinra is not recommended (see **sections 4.3** and **4.5**).

Concurrent administration of SIMPONI with abatacept

In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI and abatacept is not recommended (see **sections 4.3** and **4.5**).

Concurrent Administration with other Biological Therapeutics

There is insufficient information regarding the concomitant use of SIMPONI with other biological therapeutics used to treat the same conditions as SIMPONI. The concomitant use of SIMPONI 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.

Surgery

There is limited safety experience of SIMPONI 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 should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression

The possibility exists for TNF-blocking agents, including SIMPONI, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In Phase I RA studies, in 81 patients evaluated, there were no substantial differences between subjects receiving golimumab 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.

Live Vaccines / Therapeutic Infectious Agents

Patients treated with SIMPONI 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.

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.

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 2-fold increase in antibody titres. 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

Allergic reactions (e.g., rash, urticaria, and rarely anaphylaxis and serum sickness-like reactions) have been observed in patients treated with TNF-blocking agents. Serious allergic adverse reactions have not been reported with subcutaneous administration of SIMPONI during clinical trials. Non-serious allergic reactions associated with SIMPONI occurred in clinical trials, and included urticaria, bronchospasm and hypersensitivity. If an anaphylactic reaction or other serious allergic reactions occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity

The needle cover on the pre-filled syringe and the pre-filled syringe in the pre-filled pen is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Hypersensitivity reactions

In post-marketing experience, serious hypersensitivity reactions (including anaphylactic reaction) have been reported following SIMPONI administration. Some of these reactions occurred after the first administration of SIMPONI. If an anaphylactic or other serious allergic reaction occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy instituted.

Special populations

Use in children and adolescents

Specific studies of SIMPONI in paediatric patients have not been conducted.

Use in elderly

In the Phase 3 studies in RA, PsA, and AS, no overall differences in adverse effects (AEs), serious adverse effects (SAEs), and serious infections in patients age 65 or older (N=155) who received SIMPONI were observed compared with younger patients. 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.

Use in renal and hepatic insufficiency

Specific studies of SIMPONI have not been conducted in patients with renal or hepatic impairment.

4.5 Interactions with other medicines and other forms of interactions

No interaction studies have been performed.

Concurrent use of SIMPONI with other Biological Therapeutics

An increased risk of serious infections has been seen in clinical RA studies of other TNF blockers used in combination with anakinra or abatacept, with no added benefit; therefore, the use of SIMPONI with anakinra or abatacept is not recommended (see **sections 4.3** and **4.4**). A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker.

The combination of SIMPONI with other biological therapeutics used to treat the same conditions as SIMPONI is not recommended.

Live vaccines / Therapeutic Infectious Agents

Live vaccines should not be given concurrently with SIMPONI (see **section 4.4**).

Therapeutic infectious agents should not be given concurrently with SIMPONI (see **section 4.4**).

Methotrexate (MTX)

Although concomitant use of MTX results in higher steady-state trough concentrations of SIMPONI in patients with RA, PsA, or AS, the data do not suggest the need for dose adjustment of either SIMPONI or MTX (see **section 5.2**).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use adequate contraception and continue its use for at least 6 months after the last SIMPONI treatment.

Pregnancy

Category C

The use of SIMPONI in pregnant women is not recommended. Studies in cynomolgus monkeys have shown no untoward effects on the course of pregnancy, embryofoetal development, parturition or neonatal development, at doses achieving serum concentrations in excess of those expected with the recommended dose.

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 infants born by the treated women. Consequently, these infants may be at an 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 **sections 4.4 – Live Vaccines/Therapeutic Infectious Agents** and **4.5**).

Breast-feeding

It is unknown whether golimumab is excreted in human breast milk or absorbed systemically by infants after ingestion. Golimumab was detected in monkey breast milk at low concentrations. The mean breast milk to plasma concentration ratio was 0.002:1. Because immunoglobulins are excreted in human milk, and because of the potential effects in infants, the use of SIMPONI while breastfeeding is not recommended. Breastfeeding should be discontinued for at least 6 months after the last SIMPONI treatment.

Fertility

The potential effects of golimumab on fertility have not been investigated in animal studies.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of golimumab based on the comprehensive assessment of the available adverse event information. A causal relationship with golimumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Safety data from Phase 2 and 3 clinical trials are available from 5717 SIMPONI-treated patients including 3090 with RA, 564 with PsA, 564 with AS, 1245 with UC and 231 with severe persistent asthma.

Table 1 summarises 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 RA, AS and PsA, respectively (in 639 placebo and 1659 golimumab exposed patients).

The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA, and AS was 2% for SIMPONI-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%).

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 N=639	**SIMPONI ± DMARDs N=1659**
Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)	92 (14%)	279 (17%)
Bacterial infections (such as cellulitis)	6 (1%)	24 (1%)
Viral infections (such as influenza and herpes)	20 (3%)	75 (5%)
Bronchitis	9 (1%)	31 (2%)
Sinusitis	8 (1%)	27 (2%)
Superficial fungal infections	8 (1%)	31 (2%)
Anaemia	6 (1%)	20 (1%)

	Placebo ± DMARDs N=639	SIMPONI ± DMARDs N=1659
Allergic reactions (bronchospasm, hypersensitivity, urticaria)	7 (1%)	24 (1%)
Depression	6 (1%)	18 (1%)
Insomnia	7 (1%)	22 (1%)
Dizziness	8 (1%)	33 (2%)
Paraesthesia	3 (1%)	27 (2%)
Headache	36 (6%)	75 (5%)
Hypertension	10 (2%)	51 (3%)
Constipation	2 (0%)	18 (1%)
Dyspepsia	10 (2%)	38 (2%)
Gastrointestinal and abdominal pain	17 (3%)	56 (3%)
Alanine aminotransferase increased	18 (3%)	58 (4%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Alopecia	4 (1%)	18 (1%)
Dermatitis	7 (1%)	17 (1%)
Pruritus	10 (2%)	33 (2%)
Rash	15 (2%)	48 (3%)
Pyrexia	4 (1%)	20 (1%)
Asthenia	22 (3%)	70 (4%)
Injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia)	14 (2%)	97 (6%)
Chest discomfort	7 (1%)	17 (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).		

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Less common clinical trial adverse drug reactions (<1%)

Adverse drug reactions that occurred at rates less than 1% during the SIMPONI clinical trials included the following events listed by system organ class:

Infections and infestations:

Sepsis, including septic shock, tuberculosis, lower respiratory tract infection (such as pneumonia), opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), pyelonephritis, abscess, arthritis bacterial, bursitis infective, Hepatitis B reactivation

Neoplasms benign, malignant and unspecified:

Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus), lymphoma, leukaemia, paediatric malignancy

Investigations:

Neutrophil count decreased

Blood and lymphatic system disorders:

Leukopaenia (including neutropaenia), anaemia, thrombocytopaenia, pancytopaenia, aplastic anaemia*

Endocrine disorders:

Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)

Metabolism and nutrition disorders:
Blood glucose increased, lipids increased

Nervous system disorders:
Demyelinating disorders (central and peripheral), balance disorders, dysguesia

Eye disorders:
Visual disorders (such as blurred vision and decreased vision acuity), conjunctivitis, eye allergy (such as pruritus and irritation)

Cardiac disorders:
Congestive heart failure (new onset or worsening), arrhythmia, ischaemic coronary artery disorders

Vascular disorders:
Thrombosis (such as deep venous and aortic), Raynaud's phenomenon, flushing, vasculitis (systemic)

Respiratory, thoracic and mediastinal disorders:
Asthma and related symptoms (such as wheezing and bronchial hyperactivity), interstitial lung disease

Gastrointestinal disorders:
Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastroesophageal reflux disease, stomatitis, constipation.

Hepatobiliary disorders:
Cholelithiasis, hepatic disorders

Skin and subcutaneous tissue disorders:
Psoriasis (new onset, palmar/plantar, and pustular), urticaria, vasculitis (cutaneous)

Musculoskeletal and connective tissue disorders:
Lupus-like syndrome

Renal and urinary disorders:
Bladder disorders, renal disorders

Reproductive system and breast disorders:
Breast disorders, menstrual disorders

General disorders and administration site conditions:
Impaired healing

Injury, poisoning and procedural complications:
Bone fractures

Other clinical trial adverse drug reactions in ulcerative colitis clinical trials

In the Phase 2/3 trials in UC evaluating 1240 SIMPONI-treated patients, no new adverse drug reactions were identified and the frequency of adverse drug reactions was similar to the safety profile observed in patients with RA, PsA and AS.

Post-marketing Experience

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with SIMPONI and precise estimates of incidence cannot be made due to voluntary reporting from a population of uncertain size. These adverse drug reactions are ranked by frequency, using the following convention: Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and <1/100), rare (≥ 1/10,000 and < 1/1000), very rare (<1/10,000, including isolated reports), not known (cannot be estimated from the available data).

System Organ Class	Adverse Drug Reaction	Frequency
General Disorders and Administration Site Conditions	Infusion-related reaction	Uncommon
Neoplasm Benign and Malignant	Melanoma, Merkel cell carcinoma Hepatosplenic T-cell lymphoma*	Rare Not known
Immune System Disorders	Serious systemic hypersensitivity reactions (including anaphylactic reaction) Sarcoidosis	Rare
Skin and Subcutaneous Tissue Disorders	Bullous skin reactions Lichenoid reactions Skin exfoliation	Uncommon Rare
* observed with other TNF-blocking agents		

Infections (see section 4.4)

In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of SIMPONI-treated patients (incidence per patient-year: 0.61; 95% CI: 0.55, 0.67) compared with 10.7% of control patients (incidence per patient-year: 0.55; 95% CI: 0.44, 0.63). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per patient year of upper respiratory tract infections was 0.35 events; 95% CI: 0.34, 0.36, for SIMPONI-treated patients.

In the controlled period of pivotal trials, infections were observed in 22.8% of SIMPONI-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 controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per patient year of infections was 0.81 events; 95% CI: 0.79, 0.83, for SIMPONI-treated patients.

Serious infections observed in SIMPONI-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 1.2% of SIMPONI-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 SIMPONI 100 mg group, 0.03; 95% CI: 0.01, 0.06 for the SIMPONI 50 mg group and 0.04; 95% CI: 0.02, 0.07 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of SIMPONI-treated patients compared with 1.5% of control 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 SIMPONI 100 mg compared with patients receiving SIMPONI 50 mg. The incidence per patient-year of all serious infections was 0.04; 95% CI: 0.04, 0.05, in patients receiving SIMPONI 100 mg and 0.03; 95% CI: 0.02, 0.03, in patients receiving SIMPONI 50 mg. These results may be confounded by the designs of the pivotal trials and different durations of follow-up across treatment groups.

Malignancies **(see section 4.4)**

Lymphoma

The incidence of lymphoma in SIMPONI treated patients during the pivotal trials was higher than expected in the general population.

In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving SIMPONI 100 mg compared with patients receiving SIMPONI 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. Lymphoma was diagnosed in 7 subjects (1 in the golimumab 50 mg treatment groups and 6 in the golimumab 100 mg treatment groups) with an incidence (95%, CI) per 100 subject-years of follow up of 0.04 (0.00, 0.24) and 0.18 (0.06, 0.38) events for SIMPONI 50 mg and 100 mg respectively. The majority of lymphomas occurred in GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease.

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 SIMPONI and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

Through approximately 3 years of follow-up of the Phase 2b and Phase 3 studies in RA, PsA and AS, among patients receiving SIMPONI, non-melanoma skin cancer was diagnosed in 28 subjects (10 in SIMPONI 50 mg and 18 in SIMPONI 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.49 (0.33, 0.71) events for SIMPONI.

Through approximately 3 years of follow-up, of the Phase 2b and Phase 3 studies in RA, PsA and AS, among patients receiving SIMPONI, malignancies besides non-melanoma skin cancer and lymphoma were diagnosed in 32 subjects (18 in SIMPONI 50 mg and 14 in SIMPONI 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.56 (0.38, 0.79) events for SIMPONI.

Cases reported in clinical studies in asthma

In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies were reported in the combined golimumab treatment group (N=230) and none in the placebo treatment group (N=79). Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

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

Demyelinating Disorders (see section 4.4)

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 SIMPONI 100 mg compared with patients receiving SIMPONI 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.

Liver enzyme elevations

In controlled Phase 3 trials in RA, PsA and AS through Week 16, ALT elevations were seen more commonly than AST elevations. Among those subjects with normal ALT levels at baseline, proportions of ALT elevations were in general greater for treatment regimens that included MTX compared with treatment regimens that did not.

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In the controlled period of RA and PsA pivotal trials, mild ALT

elevations (> 1 and < 3x ULN) occurred in similar proportions of SIMPONI and control patients (22.1% to 27.4% of patients); in the AS study, more SIMPONI-treated patients (25.6%) than control patients (3.9%) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in the SIMPONI-treated and control patients. In the AS pivotal trial, the incidence of mild ALT elevations was higher in SIMPONI-treated patients than in control patients.

In the controlled period of the UC pivotal trials of SIMPONI induction, mild ALT elevations (>1 and <3 x ULN) occurred in similar proportions of SIMPONI-treated and control patients (8.0% to 6.9%, respectively). In 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 SIMPONI.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5x 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, the incidence of ALT elevations ≥ 5x ULN was similar in both SIMPONI-treated and control patients. The majority of these elevations were asymptomatic.

In the controlled periods of the pivotal UC trials of SIMPONI, ALT elevations ≥ 5 x ULN occurred in similar proportions of SIMPONI-treated patients compared to placebo patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials, with a mean follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving SIMPONI.

Hepatobiliary adverse events

In controlled Phase 3 trials in RA, PsA and AS through Week 16, the proportions of patients with hepatobiliary adverse events were 0.8% in the SIMPONI-treated patients and 0.6% in control patients.

Psoriasis: New-Onset and Exacerbations

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including SIMPONI. Cases of exacerbation of pre-existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalisation. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of SIMPONI should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Injection site reactions

In the controlled periods of the pivotal trials, 5.1% of SIMPONI-treated patients had injection site reactions compared with 2.0% in control patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

In controlled phase 2 and 3 trials in RA, PsA, AS, UC and severe persistent asthma, no patients treated with SIMPONI developed anaphylactic reactions deemed to be related to golimumab.

Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies

In the controlled and uncontrolled periods of the pivotal trials at 1 year of follow up, 3.5% of SIMPONI-treated patients and 2.3% of control patients were newly ANA-positive (at titres of

1:160 or greater) compared with baseline. The frequency of anti-dsDNA antibodies at 1 year of follow up in patients anti-dsDNA negative at baseline was 1.1%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of actions

Golimumab is a human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology. It forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human tumour necrosis factor (TNF), which prevents the binding of TNF to its receptors. Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis (RA), as well as spondyloarthropathies such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS), and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

Pharmacodynamics

The binding of human TNF by golimumab was shown to neutralise 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.

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 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-pyridinolin (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.

Clinical Efficacy

Rheumatoid arthritis

The efficacy and safety of SIMPONI were evaluated in three multi-centre, randomised, 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. 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. Placebo-controlled efficacy data were collected and analysed through week 24.

The study GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX. This study excluded patients who previously received TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure (CHF), demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancers. Patients were randomised 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 use of disease-modifying anti-rheumatic drugs (DMARDs) including sulfasalazine (SSZ), hydroxychloroquine (HCQ), cytotoxic agents, or other biologicals was prohibited. All patients receiving placebo + MTX received SIMPONI 50mg + MTX 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 in which patients continued treatment with either SIMPONI 50 mg + MTX, SIMPONI 100mg + MTX, or SIMPONI 100mg monotherapy. After the last patient completed the week 52 visit and the trial was unblinded, patients receiving SIMPONI 50 mg could have the dose increased to 100 mg at the discretion of the investigator, and patients who were receiving SIMPONI monotherapy could have MTX added. Efficacy data were collected and analysed through week 256.

The study GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. This study excluded patients with serious or chronic infections, history of CHF, demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo (N=150), SIMPONI 50 mg (N=147), or SIMPONI 100 mg (N=148). Patients were allowed to continue concomitant DMARD therapy with MTX, SSZ, and/or HCQ during the study. Discontinuation of prior anti-TNF therapies could have been for reasons including lack of efficacy (58%), intolerance (17%), and/or reasons other than safety or efficacy (40%). Other than MTX, SSZ, and HCQ, the use of other DMARDs including cytotoxic agents or other biologics was prohibited. At week 24, patients entered the long-term extension phase in which patients continued treatment with either SIMPONI 50 mg or SIMPONI 100 mg; all patients receiving placebo began receiving SIMPONI 50 mg at week 24. After the last patient completed the week 24 visit and the trial was unblinded, patients receiving SIMPONI 50 mg could have their dose increased to 100 mg at the discretion of the investigator. Efficacy data were collected and analysed through week 256.

The study GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve. This study excluded patients who previously received TNF blocking agents, and patients with serious or chronic infections, history of CHF, demyelinating disorders or history of malignancy with exception of treated non-melanoma skin cancers. Patients were randomised 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 use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited. At week 52, patients receiving placebo + MTX who had at least 1 tender or swollen joint began receiving SIMPONI 50 mg + MTX. Patients who had no swollen or tender joints at week 52 continued to receive placebo + MTX after week 52. At week 52, patients entered the long-term extension phase in which the majority of patients continued

treatment with either SIMPONI 50 mg + MTX, SIMPONI 100 mg + MTX, or SIMPONI 100 mg monotherapy. The trial remained double-blind until all patients had completed 52 weeks of treatment. After the last patient completed the week 52 visit and the trial was unblinded, patients receiving SIMPONI 50 mg could have the dose increased to 100 mg at the discretion of the investigator, and patients who were receiving SIMPONI 100 mg monotherapy could have MTX added. Efficacy data were collected and analysed through week 256.

In GO-AFTER, GO-FORWARD, and GO-BEFORE, the median duration of RA disease was 9.4, 5.7, and 1.2 years, respectively.

The co-primary endpoint in GO-FORWARD and the primary end-point in GO-AFTER was the percentage of patients achieving an ACR 20 response at Week 14. The other co-primary endpoint in GO-FORWARD was the improvement from baseline in the Health Assessment Questionnaire (HAQ) score at Week 24 and the major secondary endpoint included change from baseline in van der Heijde-modified Sharp (vdH-S) score at week 24. The primary co-endpoints for GO-BEFORE was the percentage of patients achieving ACR 50 response at Week 24, and the change from baseline in vdH-S score at week 52. In addition to these endpoints, additional assessments of the impact of SIMPONI treatment on the signs and symptoms of arthritis, physical function and health-related quality of life were performed.

Key results for the 50 mg dose are shown in **Tables 2**, **3** and **4** below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens in each of the Phase 3 RA studies through Week 104 in GO-FORWARD and GO-BEFORE and through Week 24 in GO-AFTER. In GO-FORWARD and GO-BEFORE, the SIMPONI 100 mg monotherapy groups were not statistically different from the MTX monotherapy groups in ACR response. In each of the three RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg SIMPONI doses at the discretion of the physician.

Signs and symptoms: In all phase 3 RA studies, a greater percentage of SIMPONI-treated patients achieved ACR and Disease Activity Score 28 (DAS28) responses at Weeks 14 and 24 versus the control groups. Responses were observed at the first assessment (Week 4) after the initial SIMPONI administration.

Table 2: Key efficacy outcomes from GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		**GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)**		**GO-BEFORE Active RA, MTX Naïve**	
	Placebo + MTX	**SIMPONI 50 mg + MTX**	**Placebo**	**SIMPONI 50 mg**	**Placebo + MTX**	**SIMPONI 50 mg + MTX**
N[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	33%	55%*	18%	35%*	NA	NA
Week 24	28%	60%*	16%	31% p=0.002	49%	62% p=0.028
ACR 50						
Week 14	10%	35%*	7%	15% p=0.021	NA	NA
Week 24	14%	37%*	4%	16%*	29%	40% p=0.042[b]
ACR 70						
Week 14	4%	14% p=0.008	2%	10% p=0.005	NA	NA

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	**SIMPONI 50 mg + MTX**	**Placebo**	**SIMPONI 50 mg**	**Placebo + MTX**	**SIMPONI 50 mg + MTX**
Week 24	5%	20%*	2%	9% p=0.009	16%	24% p=0.064
DAS28 response [c]						
Week 14	50%	72%*	27%	56%*	NA	NA
Week 24	42%	73%*	21%	45%*	61%	75% p=0.007
DAS28 remission [c]						
Week 14	5%	27%*	1%	9%	NA	NA
Week 24	7%	27%*	2%	10% p=0.005	28%	26% p=0.129

a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.

*: $p \leq 0.001$

b: This p-value (50 mg vs. placebo) should not be interpreted as implying statistical significance, because the p-value for the primary analysis (combined SIMPONI 50 mg and 100 mg groups vs. placebo) was not statistically significant (p=0.053) and a hierarchical approach was used for the statistical analyses.

c: Using CRP

NA: Not applicable, as data was not collected at week 14 in this study.

In GO-FORWARD and GO-BEFORE, the proportions of patients achieving an ACR ACR 20, ACR 50 or ACR 70 response were maintained through Week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of ACR 20, ACR 50 or ACR 70 responses were observed from Week 104 through Week 256.

The proportion of patients achieving a DAS28 (using CRP) response at week 52 was greater for those patients treated with SIMPONI 50mg + MTX compared with those who received placebo + MTX (72% compared with 61%; p=0.035). Similarly, statistically significant results were observed when DAS28 (using ESR) response was assessed. The percentage of patients achieving a DAS28 (using CRP) remission at week 52 was greater for those patients treated with SIMPONI 50mg + MTX compared with those who received placebo + MTX (35% compared with 23%; p=0.018). The proportions of patients achieving a DAS28 (using CRP) response or remission at week 52 were maintained at week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of DAS28 response or remission (using CRP) were observed from Week 104 through Week 256.

In GO-FORWARD and GO-AFTER all individual components of the ACR response criteria [number of tender and swollen joints, patient's assessment of pain, patient's and physician's global assessment of disease activity, disability index (as measured by HAQ) and CRP] were significantly improved in the SIMPONI-treated patients versus control patients ($p < 0.001$). The results of the components of the ACR response criteria are shown in **Table 3**.

Table 3: Percent improvement in components of ACR Response in RA trials GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	SIMPONI 50 mg + MTX*	Placebo	SIMPONI 50 mg*	Placebo + MTX	SIMPONI 50 mg + MTX
N[a]	133	89	150	147	160	159
Number of swollen joints						
Baseline	12.0	13.0	14	15	11	13
Week 14	38 %	62 %	20 %	44 %	NA	NA
Week 24	32 %	72 %	1 %	33 %	67 %	76 % (p=0.127)
Number of tender joints						
Baseline	21.0	26.0	26	28	26	26
Week 14	30 %	60 %	6 %	34 %	NA	NA
Week 24	21 %	62 %	-7 %	29 %	57 %	67 % (p=0.023)
Patient's assessment of pain						
Baseline	5.7	6.1	7	7.0	7	7
Week 14	18 %	55 %	12 %	25 %	NA	NA
Week 24	15 %	50 %	4 %	25 %	44 %	52 % (p=0.028)
Patient's global assessment of disease activity						
Baseline	5.3	6.0	6.7	6.8	6	6
Week 14	15 %	45 %	8 %	29 %	NA	NA
Week 24	17 %	48 %	2 %	22 %	37 %	50 % (p=0.042)
Physician's global assessment of disease activity						
Baseline	5.7	6.1	6.3	6.5	6	6
Week 14	35 %	55 %	12 %	38 %	NA	NA
Week 24	39 %	62 %	10 %	35 %	63 %	67 % (p=0.206)
HAQ score						
Baseline	1.25	1.38	1.75	1.63	1.50	1.50
Week 14	10 %	29 %	0 %	13 %	NA	NA
Week 24	7 %	31 %	0 %	11 %	37 %	44 % (p=0.141)
CRP (mg/L)						
Baseline	8.0	10.0	100	9.0	14.0	13.0
Week 14	2 %	44 %	0 %	37 %	NA	NA
Week 24	0 %	39 %	0 %	15 %	43 %	57 % (p=0.002)

*: $p \leq 0.001$ for all comparisons.

a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.

NA: Not applicable, as data was not collected at week 14 in this study.

In GO-FORWARD and GO-BEFORE, the percent improvement in the ACR components measured (swollen joint count, tender joint count and CRP) observed at week 24 was

maintained at week 52 and week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of percentage improvement in the ACR components measured (swollen joint count, tender joint count and CRP) were observed from Week 104 through Week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving SIMPONI 50 mg than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies. This difference was statistically significant for patients who reported discontinuation of one or more prior anti-TNF therapies because of lack of efficacy. In this patient group, 35% of the patients treated with SIMPONI 50 mg versus 18% of those in the control group achieved an ACR 20 at Week 14 (p=0.009). At Week 24 the percentages were 29% compared with 16%, respectively (p=0.035).

Major clinical response, defined as maintenance of an ACR 70 response over a continuous 6-month period was measured in GO-BEFORE. At week 52, 15% of patients in the SIMPONI 50mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group (p=0.018).

Radiographic response: The progression of structural joint damage (erosions and joint space narrowing) in both hands and feet was evaluated in GO-BEFORE at week 52 as a co-primary endpoint and in GO-FORWARD at week 24 as a major secondary endpoint. 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.

In GO-BEFORE, SIMPONI 50 mg + MTX resulted in significantly less radiographic progression than placebo + MTX, as assessed by total vdH-S score (p = 0.015) Results are shown in **Table 4**.

Table 4: Radiographic change from baseline at week 52 in RA trial GO-BEFORE

	Placebo + MTX (N = 160)[a]	**SIMPONI 50 mg + MTX (N = 159)[a]**
Total score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.74 (2.8)	0.48 (2.1)
JSN score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)*

[a] N reflects randomized patients

* $p < 0.05$

Values are mean (standard deviation) in total vdH-S score

In GO-BEFORE, SIMPONI 50mg + MTX demonstrated significant inhibition in radiographic progression compared with placebo + MTX among patients with abnormal (> 1.0 mg/dL) CRP (mean (SD) change from baseline in total vdH-S score 1.3 (7.0) versus 2.2 (5.6) respectively, p=0.010). A greater number of patients in the SIMPONI 50mg + MTX group (71%) had no new erosions in uninvolved joints at baseline compared to MTX alone (54%). There was a significantly greater number of subjects in the SIMPONI 50mg + MTX group without an increase from baseline in total vdH-S score compared with the placebo + MTX group (71% versus 54% respectively, p=0.003).

Inhibition of radiographic progression observed at Week 52 was maintained at Week 104. Among patients remaining in the study and treated with SIMPONI, inhibition of radiographic progression was similar from Week 104 through Week 256.

In GO-FORWARD changes from baseline in total vdH-S score at week 24 in all treatment groups were minimal. No significant difference in the change from baseline in total vdH-S score at week 24 was observed in the SIMPONI + MTX groups compared with the placebo +MTX groups.

Physical function and health-related quality of life: Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ. In these studies, SIMPONI demonstrated clinically meaningful and statistically significant improvement in HAQ versus control from baseline to week 24 (see **Table 5**).

Table 5: Improvement in HAQ from GO-FORWARD and GO-AFTER

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent	
	Placebo + MTX	**SIMPONI 50 mg + MTX**	**Placebo**	**SIMPONI 50 mg**
N[a]	133	89	150	147
HAQ baseline score				
Mean ± SD	1.32 ± 0.70	1.41 ± 0.69	1.63 ± 0.63	1.58 ± 0.65
Median	1.25	1.38	1.75	1.63
Improvement in HAQ				
Week 14 Mean ± SD	0.16 ± 0.49	0.42 ± 0.38	NA	NA
Median	0.13	0.38 [b]	NA	NA
Week 24 Mean ± SD	0.13 ± 0.58	0.47 ± 0.55	0.03 ± 0.50	0.23± 0.50
Median	0.13	0.38	0.00	0.13

a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
b: $p < 0.001$
NA: Not applicable, as this data was not collected at week 14 in this study.

In GO-AFTER and GO-FORWARD, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at week 24: 44% vs. 28%, 65% vs. 35%, respectively. In GO-AFTER, 61% of subjects in the SIMPONI 50 mg + MTX group, who had a clinically meaningful improvement (>0.22) in HAQ from baseline to Week 24, maintained this level of improvement at Week 100. In GO-FORWARD, 87% of subjects in the SIMPONI 50 mg + MTX group, who had a clinically meaningful improvement (>0.22) in HAQ from baseline to Week 24, maintained this level of improvement at Week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of improvement in HAQ was observed from Week 104 through Week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with SIMPONI versus placebo. The improvement in SF-36 PCS score observed at week 24 was maintained at week 52 and week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of improvement in SF-36 PCS score was observed from Week 104 through Week 256.

In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in self-reported productivity and in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F). Among patients remaining in the study and treated with SIMPONI, similar rates of improvement in HAQ were observed from Week 24 through Week 256.

Psoriatic arthritis

The safety and efficacy of SIMPONI were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Patients with each sub-type 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%). The median duration of PsA disease was 5.1 years. This study excluded patients previously treated with TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure, demyelinating disorders or a history of malignancy with the exception of treated basal skin cancer. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg, with or without MTX, every 4 weeks. Patients were randomly assigned to placebo (N=113), SIMPONI 50 mg (N=146), and SIMPONI 100 mg (N=146). All patients receiving 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 in which patients continued treatment with either SIMPONI 50 mg, or SIMPONI 100 mg. After the last patient completed treatment the week 52 visit and the trial was unblinded, patients receiving SIMPONI 50 mg could have the dose increased to 100 mg at the discretion of the investigator. The co-primary endpoints were the percentage of patients achieving ACR 20 response at Week 14 and change from baseline in total PsA modified vdH-S score at week 24. Efficacy data were collected and analysed through week 256.

Signs and symptoms: Key results for the 50 mg dose are shown in **Table 6** below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens in the Phase 3 PsA study through Week 104. By study design, patients in the long-term extension may have switched between the 50mg and 100mg SIMPONI doses at the discretion of the study physician.

Table 6: Key efficacy outcomes from GO-REVEAL

	Placebo	SIMPONI 50 mg*
N[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	9 %	51 %
Week 24	12 %	52 %
ACR 50		
Week 14	2 %	30 %
Week 24	4 %	32 %
ACR 70		
Week 14	1 %	12 %
Week 24	1 %	19 %
DAS 28		
Week 14	24 %	69 %
Week 24	22 %	65 %
PASI 75[b]		
Week 14	3 %	40 %
Week 24	1 %	56 %
HAQ Baseline score		
Mean ±SD	1.03 ± 0.55	0.98 ± 0.65
Median	1.00	1.00

		Placebo	SIMPONI 50 mg*
Improvement in HAQ			
Week 14	Mean ± SD	0.04 ± 0.44	0.31 ± 0.50
	Median	0.00	0.25
Week 24	Mean ± SD	-0.01 ± 0.49	0.33 ± 0.55
	Median	0.00	0.25
*: $p < 0.05$ for all comparisons; p-value calculations are based on comparisons of median values for continuous variables a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint b: Based on the subset of patients with ≥ 3% body surface area (BSA) involvement at baseline			

Improvements in key measures of disease activity were observed at the first assessment (Week 4) after the initial SIMPONI administration and were maintained through Week 24. Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes including polyarticular arthritis with no rheumatoid nodules, asymmetric peripheral arthritis, DIP arthritis, and spondylitis with peripheral arthritis. The number of patients with arthritis mutilans was too small to allow meaningful assessment. Responses observed in the SIMPONI treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to SIMPONI 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively.

At week 24, improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the SIMPONI-treated patients. The median percent improvement in enthesitis and dactylitis scores observed at week 24 were maintained through week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of median percent improvement in enthesitis and dactylitis scores were observed from Week 104 through Week 256. Proportions of patients with PASI 50, 75 or 90 responses observed at week 24 were maintained through week 104. Among patients remaining in the study and treated with SIMPONI, similar rates of PASI 50, 75 or 90 were observed from Week 104 through Week 256. Similarly, SIMPONI-treated patients also demonstrated significant improvement in skin and nail psoriasis as assessed by the Psoriatic Area and Severity Index (PASI), percent change from baseline in the Nail Psoriasis Severity Index (NAPSI), and improvement in nail Physician Global Assessment (PGA).

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. At week 24, SIMPONI 50 mg significantly inhibited the progression of structural damage compared with placebo. Results are shown in **Table 7**. Patients treated with SIMPONI with or without MTX had less progression than patients receiving placebo with or without MTX.

Table 7: Radiographic change from baseline at week 24 in PsA trial GO-REVEAL

	Placebo (N = 113)[a]	SIMPONI 50 mg (N = 146)[a]
Total score		
Baseline	18.2 (27.8)	23.9 (35.4)
Change from baseline	0.27 (1.3)	-0.16 (1.3)*
Erosion score		
Baseline	10.6 (16.1)	13.7 (19.6)
Change from baseline	0.32 (0.9)	-0.09 (0.9)**
JSN score		
Baseline	7.5 (12.5)	10.1 (16.8)

	Placebo (N = 113)[a]	SIMPONI 50 mg (N = 146)[a]
Change from baseline	-0.03 (0.7)	-0.03 (0.6)
[a] N reflects randomized patients actual number of patients for each analysis may vary * p = 0.011 **p < 0.001 Values are mean (standard deviation) in total PsA modified vdH-S score		

A significantly greater number of patients in the SIMPONI 50 mg group had no new erosions or no new joint space narrowing (JSN) in joints that were uninvolved at baseline compared to placebo (see **Table 8**).

Table 8: New erosions and JSN in previously uninvolved joints at week 24 in PsA trial GO-REVEAL

	Placebo (N = 113)[a]	SIMPONI 50 mg (N = 146)[a]	p-value
Patients with at least 1 previously uninvolved joint	102	132	
Patients with no new erosions	73 (72%)	115 (87%)	0.003
Patients with at least 1 previously uninvolved joint	102	132	
Patients with no new JSN	90 (88%)	128 (97%)	0.008
[a] N reflects randomized patients Values are number (%)			

There was a significantly greater number of patients in the SIMPONI 50 mg group without an increase from baseline in total PsA modified vdH-S score compared with the placebo group (79% versus 63% respectively, p=0.007).

The effect of SIMPONI on radiographic progression was maintained at week 104. For the 114 patients randomised to SIMPONI 50 mg who continued SIMPONI treatment after week 52, 77% had a change from baseline in total PsA modified vdH-S score ≤0 at week 104. Among patients remaining in the study and treated with SIMPONI, a similar effect on radiographic progression was observed from Week 104 through Week 256.

Physical function and health-related quality of life: SIMPONI treatment resulted in significant improvement in physical function as assessed by HAQ, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Self-reported productivity was significantly improved and time lost from work by caregivers was significantly reduced.

Among patients who remained on the SIMPONI treatment to which they were randomised at study start, improvement in physical function and health-related quality of life measures were maintained through week 256.

Ankylosing spondylitis

The safety and efficacy of SIMPONI were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a visual analog score (VAS) for total back pain of ≥4, on a scale of 0 to 10 cm). Patients enrolled in this study had symptoms of active disease despite current or previous NSAID or DMARD therapy. The median duration of AS disease was 5.6 years. Patients with complete ankylosis of the spine were excluded from study participation. This study also excluded patients previously treated with TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure, demyelinating disorders or a history of

malignancy with the exception of treated non-melanoma skin cancer. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Patients were randomly assigned to placebo (N=78), SIMPONI 50 mg (N=138) and SIMPONI 100 mg (N=140). The primary endpoint was the percentage of patients achieving a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS 20) response criteria at Week 14. Efficacy data were collected and analysed through week 256.

Key results for the 50 mg dose are shown in **Table 9** below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens in the Phase 3 AS study through Week 24. By study design, patients in the long term extension may have switched between the 50 mg and 100 mg SIMPONI doses at the discretion of the study physician.

Table 9: Key efficacy outcomes from GO-RAISE

	Placebo	SIMPONI 50 mg*
N[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	22 %	59 %
Week 24	23 %	56 %
ASAS 40		
Week 14	15 %	45 %
Week 24	15 %	44 %
ASAS 5/6		
Week 14	8 %	50 %
Week 24	13 %	49 %
BASDAI 50		
Week 14	15 %	46 %
Week 24	15 %	51 %
BASDAI 70		
Week 14	5 %	29 %
Week 24	8 %	30 %
BASDAI 90		
Week 14	1 %	10 %
Week 24	1 %	15 %
BASFI (0-10): median change from baseline		
Baseline (median)	4.9	5.0
Week 14	0.1	-1.4
Week 24	0.4	-1.6

*: $p \leq 0.001$ for all comparisons with the exception of BASDAI 90 at Week 14 where $p = 0.017$

a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Compared with placebo, SIMPONI treatment resulted in a significant improvement in signs and symptoms as demonstrated by the ASAS and BASDAI scores at Weeks 14 and 24. Patients treated with SIMPONI achieved significantly greater improvement in all ASAS 20 components compared with placebo. Improvements in key measures of disease activity were observed at the first assessment (Week 4) after the initial SIMPONI administration and were maintained through week 24. Consistent efficacy was seen in patients regardless of HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14. A greater percentage of patients treated with SIMPONI achieved a low level of disease activity (defined as a value < 2 on a scale of 0-10 cm in each of the four ASAS 20 response

parameters) at week 14 (23%) compared to patients treated with placebo (5%, $p < 0.001$), and was maintained through week 24.

Among patients remaining in the study and treated with SIMPONI, the proportion of patients with an ASAS 20 and ASAS 40 response were similar from Week 24 through Week 256. Similar rates of improvement in ASAS 20 components measured (patient's global assessment of disease activity, total back pain and night back pain) were also observed from Week 24 to Week 256. Similar rates of change from baseline in BASDAI were also observed from Week 24 to Week 256.

SIMPONI treatment resulted in significant improvements in physical function as assessed by changes from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 14 and 24. Median improvement in 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 through week 24 in SIMPONI-treated patients. Among patients remaining in the study and treated with SIMPONI, similar rates of improvement in physical function were observed from Week 24 through Week 256.

Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24. Among patients remaining in the study and treated with SIMPONI, similar rates of mean improvement in physical function on the SF-36 PCS were observed from Week 24 through Week 256. Significant improvements were also observed in sleep (as measured by Jenkins Sleep Evaluation Questionnaire) and self-reported productivity.

Ulcerative Colitis

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

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or 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 randomised to one of 4 treatment groups: 400 mg of SIMPONI administered subcutaneously (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, 761 patients were randomised 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. The primary endpoint was clinical response at Week 6. The major secondary endpoints were clinical remission, mucosal healing, and the improvement in the IBDQ score, all at Week 6.

The maintenance study (PURSUIT-Maintenance) evaluated 456 patients who achieved clinical response from previous induction with SIMPONI. 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. The primary endpoint 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. Patients who completed the maintenance study through Week 54 continued treatment in a study extension, with efficacy evaluated through Week 216.

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. Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1.

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 standardised non-disease specific instrument for describing and valuing health related quality of life.

Approximately 63% 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).

Table 10: Key efficacy outcomes from PURSUIT-Induction and PURSUIT-Maintenance studies

PURSUIT-Induction Study			
	Placebo N=251	**SIMPONI 200/100 mg N=253**	**p value[a]**
Patients in clinical response[b] at week 6	30.3%	51.0%	<0.0001
Patients in clinical remission[c] at week 6	6.4%	17.8%	<0.0001
Patients with mucosal healing[d] at week 6	28.7%	42.3%	0.0014
Change from baseline in IBDQ score at week 6 (mean ± SD)	14.8 ± 31.25	27.0 ± 33.72	<0.0001
Greater than 20-point improvement from baseline in IBDQ at week 6	35.5%	50.6%	0.0006
Improvement in pain/discomfort dimension of EQ-5D	15.1%	30.0%	<0.0001
Mean increase in SF-36 physical component summary score	2.51	4.51	0.0009
SF-36 mental component summary score	1.60	4.57	0.0017

PURSUIT-Maintenance Study			
	Placebo N=154	**SIMPONI 100 mg N=151**	**p value**
Maintenance of response (Patients in clinical response through Week 54)[e]	31.2%	49.7%	<0.001
Sustained remission (Patients in clinical remission at both Week 30 and Week 54)[f]	15.6%	27.8%	0.004
Sustained mucosal healing (Patients with mucosal healing at both Week 30 and Week 54)[d]	26.6%	42.4%	0.002

a P value for SIMPONI treatment group vs placebo

b Defined as a decrease from baseline 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

c Defined as a Mayo score ≤ 2 points, with no individual subscore >1

d Defined as 0 or 1 on the endoscopy subscore of the Mayo score.

e 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 response was in a state of continuous clinical response at each evaluation through Week 54.

f 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.

In 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.

Among the 35% of patients (160/456) in clinical remission at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical remission at both Week 30 and Week 54 were greater in the SIMPONI 100 mg group (38.9%, 21/54) compared with the placebo group (24.1%, 13/54, p=0.098). The median time to loss of clinical remission was greater than 54 weeks in the 100 mg group (more than half of the subjects had not met the criteria for loss of clinical remission by Week 54) and 27 weeks in the placebo group.

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients in clinical remission and not receiving concomitant corticosteroids at Week 54 was similar in the 100-mg group (23.2%, 19/82) compared with the placebo group (18.4%, 16/87). However, post hoc analyses showed the proportion of patients who maintained clinical response through Week 54 and were not receiving concomitant corticosteroids at Week 54 was numerically greater, in the 100-mg group (30.5%, 25/82) compared with the placebo group (20.7%, 18/87). Further, the proportion of patients who had eliminated corticosteroids by Week 54 was numerically greater in the 100-mg group (32.9%, 27/82) compared with the placebo group (21.8%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid-free was generally maintained through Week 216.

Among patients with a greater than 20-point improvement in IBDQ at the start of PURSUIT-Maintenance from Week 0 of the induction study, a greater proportion of patients in the SIMPONI 100 mg group maintained improvement in IBDQ through Week 54, 40.0%, compared with the placebo group, 27.8%; p = 0.051.

There is no experience of the use of SIMPONI in patients with UC who have previously received other TNF antagonists.

Immunogenicity

Antibodies to golimumab, nearly all neutralising *in vitro*, were detected in 4.3% (57/1322) of SIMPONI treated patients across the Phase 3 RA, PsA and AS studies through week 24, and similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving SIMPONI without MTX (approximately 2% [14/719] versus 7% [43/603], respectively).

Following SC administration in UC patients, antibodies to SIMPONI were detected in 2.7% of SIMPONI-treated patients through week 54. Sixty-eight percent of antibody-positive patients had neutralizing antibodies *in vitro*. 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).

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

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

5.2 Pharmacokinetic properties

Following subcutaneous (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. A SC injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL. Both C_{max} 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. Golimumab exhibited dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a

single intravenous (IV) dose. Following a single IV administration over the same dose range in patients with RA, mean systemic clearance of golimumab was estimated to be 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg, which indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be 12 ± 3 days in healthy subjects and similar half-life values were observed in patients with RA, PsA, AS or ulcerative colitis (UC). 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 pharmacokinetics following a SC administration, the absolute bioavailability of 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 MTX, treatment with 50 mg SIMPONI SC every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 μg/mL in RA patients with active RA despite MTX 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 and AS treated with SIMPONI 50 mg and MTX had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of golimumab, respectively, compared with those treated with SIMPONI 50 mg without MTX. The presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% (see **Clinical Efficacy - Immunogenicity**). Population pharmacokinetic analysis in patients with RA also indicated that concomitant use of MTX could reduce the apparent clearance of golimumab by 17.1%. However, concomitant use of non-steroidal anti-inflammatory drugs, oral corticosteroids or sulfasalazine (SSZ) were not found to influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg SIMPONI SC at Week 0 and 2 respectively, and maintenance doses of 100 mg SIMPONI SC 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 SC every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 1.8 ± 1.1 μg/mL. Concomitant use of immunomodulators did not have any apparent effect on steady-state trough levels of golimumab when 100 mg SIMPONI was administered SC every 4 weeks to UC patients.

Population pharmacokinetic analyses showed there was a trend toward higher apparent clearance of golimumab with increasing weight. However, subgroup analyses by weight quartiles did not demonstrate a meaningful difference in clinical efficacy between the different dose groups. Treatment with the recommended dose regimen of SIMPONI in UC patients did not result in meaningful differences in clinical efficacy among the different weight subgroups. Therefore, there is no need to adjust the dosage of SIMPONI based on the patient's weight.

Patients who developed anti-golimumab antibodies generally had increased clearance and low trough steady-state serum concentrations of golimumab (see **Clinical Efficacy - Immunogenicity**).

Phase 3 studies evaluated the safety and efficacy of SIMPONI at a dosage regimen of every 4 weeks with a prospectively allowed window of 3 to 7 days. Patients would receive a total of 13 doses over 1 year when SIMPONI is given every 4 weeks instead of 12 doses when given monthly. This results in a calculated difference in golimumab exposure of approximately 8% when administered monthly as recommended.

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

5.3 Preclinical safety data

Genotoxicity

No genotoxicity tests have been conducted with golimumab.

Carcinogenicity

Long-term animal carcinogenicity studies with golimumab have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol

Histidine

Histidine hydrochloride monohydrate

Polysorbate 80

Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

Solution for injection in pre-filled syringe

36 months when stored at 2°C to 8°C (Refrigerate. Do not freeze).

Solution for injection in pre-filled pen

24 months when stored at 2°C to 8°C (Refrigerate. Do not freeze).

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze. Do not shake.

Keep the pre-filled pen/syringe in the outer carton in order to protect it from light.

SIMPONI may be stored at room temperature up to a maximum of 25°C for a single period of up to 30 days in the original carton; after which, it should not be refrigerated again. SIMPONI must be protected from light. It should be discarded if not used within 30 days of removal from refrigeration.

6.5 Nature and contents of container

Solution for injection in pre-filled 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 **section 4.4 - Allergic reactions**).

SIMPONI is available in two strengths: 50mg of golimumab in 0.5mL and 100mg of golimumab in 1mL.

SIMPONI is available in packs of 1 or 3* pre-filled syringe(s).

Solution for injection in pre-filled pen

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 pre-filled pen called “SmartJect”.

The needle shields are manufactured from dry natural rubber containing latex (see **section 4.4 - Allergic reactions**).

SIMPONI is available in two strengths: 50mg of golimumab in 0.5mL and 100mg of golimumab in 1mL.

SIMPONI is available in packs of 1 or 3* pre-filled pen(s).

*Packs of 3 pre-filled syringes and Smartject pre-filled pens are not currently available.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of SIMPONI are given in the Patient Instruction Leaflet. Patients should be instructed to inject the full amount of SIMPONI according to the directions provided in the Patient Instruction Leaflet.

This product is for single use in one patient only. Discard any residue. Any unused product or waste material should be disposed of in accordance with local requirements.

SIMPONI contains no antimicrobial agent.

7. MEDICINE CLASSIFICATION

Prescription Medicine

8. NAME AND ADDRESS

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

50 mg pre-filled syringe or pre-filled pen: 16 December 2009

100 mg pre-filled syringe or pre-filled pen: 16 June 2016

10. DATE OF PREPARATION

27 June 2019

Summary table of changes

Section changes	Summary of new information
6.3	Extension of shelf life for pre-filled syringe from 24 to 36 months
6.4	Added storage at room temperature up to 25°C for a single period of 30 days