



SIMPONI[®]
Solution for Injection in a pre-filled syringe
Solution for Injection in a pre-filled pen,
SmartJect[®]

PRODUCT INFORMATION

NAME OF THE MEDICINE

Golimumab (rnc) CAS Registry Number: 476181-74-5

DESCRIPTION

Each 0.5 mL single-use pre-filled syringe or pre-filled pen contains 50 mg of golimumab. Each 1.0 mL single-use pre-filled syringe or pre-filled pen contains 100 mg of golimumab.

The solution is clear to slightly opalescent, colourless to light yellow. Inactive Ingredients: Sorbitol, histidine, histidine hydrochloride monohydrate, polysorbate 80 and water for injections.

PHARMACOLOGY

Golimumab is a human IgG1 κ 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. In non-radiographic axial spondyloarthritis (nr-Axial SpA), only CRP levels were evaluated. 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 TNF α 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.

Pharmacokinetics

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 \pm standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 $\mu\text{g/mL}$. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg. 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 golimumab exhibited approximately dose proportional pharmacokinetics following 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 $\mu\text{g/mL}$ in RA patients with active RA despite MTX therapy, and approximately 0.5 $\mu\text{g/mL}$ in patients with active PsA and approximately 0.6 $\mu\text{g/mL}$ 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 TRIALS, "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.

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

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 TRIALS, "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.

CLINICAL TRIALS

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 104.

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 24.

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 104.

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 endpoint 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 Disability Index (HAQ-DI) 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 co-primary 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 endpoint(s), 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 1 and 2 below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens. In GO-FORWARD and GO-BEFORE, the SIMPONI 100 mg monotherapy groups were not statistically different from the MTX monotherapy groups in ACR response.

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 and were maintained through week 24.

Table 1: 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
Week 24	5%	20%*	2%	9% p=0.009	16%	24% p=0.064
a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint. *: p ≤ 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. 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 20, 50 or 70 response were maintained through Week 104.

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 percent 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.

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-DI) 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 2.

Table 2: 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	7.1	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-DI 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	10.0	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.

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.

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 3.

Table 3: 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 randomised 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).

After week 52, most subjects randomised to placebo + MTX began receiving SIMPONI 50mg + MTX. The effect of SIMPONI + MTX on radiographic progression was maintained at week 104.

At week 104, the mean (SD) change from baseline in total vdH-S score in subjects randomised to placebo + MTX (0.94 ± 4.237) was higher than in subjects randomised to the SIMPONI 50mg + MTX treatment group (-0.03 ± 1.927)

From week 52 to week 104, minimal to no progression in total vdH-S scores was observed in the subjects randomised to placebo + MTX (0.13 ± 2.500) or in the subjects randomised to SIMPONI 50mg + MTX (-0.09 ± 1.141) treatment groups.

At week 104, the proportion of subjects with no new erosions in joints with a score of 0 at baseline was 51.2% in the placebo + MTX group and 63.1% in the SIMPONI 50mg + MTX group.

At week 104, the proportion of subjects with no new JSN in joints with a score of 0 at baseline was 83.2% in the placebo + MTX group and 91.5% in the SIMPONI 50mg + MTX group.

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: In GO-AFTER and GO-FORWARD, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to week 24: 0.23 vs. 0.03 in GO-AFTER, 0.47 vs. 0.13 in GO-FORWARD, respectively. Also in GO-AFTER and GO-FORWARD, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ-DI responders (change from baseline ≥ 0.25) at week 24: 44% vs. 28%, 65% vs. 35%, respectively. In GO-AFTER, 81% of subjects in the SIMPONI 50 mg group, who had a clinically meaningful improvement (≥ 0.25) in HAQ-DI from baseline to Week 24, maintained this level of improvement at Week 100. In GO-FORWARD, 87% of subjects in the SIMPONI 50 mg group, who had a clinically meaningful improvement (≥ 0.25) in HAQ-DI from baseline to Week 24, maintained this level of improvement at Week 104.

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.

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 104.

Signs and symptoms: Key results for the 50 mg dose are shown in Table 4 below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens.

Table 4: 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 %
PASI 75^b		
Week 14	3 %	40 %
Week 24	1 %	56 %
HAQ-DI Baseline score		
Median	1.00	1.00
Improvement in HAQ-DI		
Week 14 and 24 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. Proportions of patients with PASI 50, 75 or 90 responses observed at week 24 were maintained through week 104.

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 5. Patients treated with SIMPONI with or without MTX had less progression than patients receiving placebo with or without MTX.

Table 5: 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)
Change from baseline	-0.03 (0.7)	-0.03 (0.6)
^a N reflects randomised 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 6).

Table 6: 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
Subjects with at least 1 previously uninvolved joint	102	132	
Subjects with no new erosions	73 (72%)	115 (87%)	0.003
Subjects with at least 1 previously uninvolved joint	102	132	
Subjects with no new JSN	90 (88%)	128 (97%)	0.008
^a N reflects randomised patients			
Values are number (%)			

There was a significantly greater number of subjects 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).

Due to the short duration of the controlled portion (24 weeks) of the GO-REVEAL study, the use of early escape in the study design, and the PsA patient population included in the study, the observed changes in total vdH-S score at Week 24 resulted in a small, but statistically significant, treatment effect size for SIMPONI 50 mg.

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. In addition, 84.2% had no new erosions and 94.7% had no new joint space narrowing at week 104.

At week 104, the mean (SD) change from baseline in total vdH-S score in subjects randomised to placebo (0.08 ± 3.193) was higher than in subjects randomised to SIMPONI 50 mg (-0.39 ± 2.041).

From week 52 to week 104, minimal to no progression in total vdH-S score was observed in subjects randomised to the placebo (-0.03 ± 1.585) or SIMPONI 50 mg (-0.01 ± 0.999) treatment groups.

Physical function and health-related quality of life: SIMPONI treatment resulted in significant improvement in physical function as assessed by HAQ-DI, 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. 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 104.

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 24.

Key results for the 50 mg dose are shown in Table 7 below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens.

Table 7: 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 %
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		
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.

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. 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.

Non-radiographic axial spondyloarthritis

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with active nr-Axial SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS). Patients enrolled in this study had active disease (defined as a BASDAI ≥ 4 and a Visual Analogue Scale (VAS) for total back pain of ≥ 4 , each on a scale of 0-10 cm) despite current or previous NSAID therapy and had not previously been treated with any biological agents including anti-TNF therapy. Patients were randomly assigned to placebo or Simponi 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period in which all patients received SIMPONI 50 mg administered subcutaneously every 4 weeks through week 48 with efficacy assessments performed through week 52 and safety follow-up through week 60. Approximately 93% of patients who were receiving SIMPONI at the beginning of the open-label extension (week 16) remained on treatment through the end of the study (week 52). Analyses were performed on both the All Treated (AT, N = 197) and Objective Signs of Inflammation (OSI, N = 158, defined by elevated CRP and/or evidence of sacroiliitis on MRI at baseline) populations. Placebo-controlled efficacy data were collected and analysed through week 16.

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

The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 8 and described below.

Table 8: Key efficacy outcomes from GO-AHEAD at week 16

Improvements in signs and symptoms				
	All treated population (AT)		Objective signs of inflammation population (OSI)	
	Placebo	SIMPONI 50 mg	Placebo	SIMPONI 50 mg
n ^a	100	97	80	78
Responders, % of patients				
ASAS 20 ^b	40%	71%**	38%	77%**
Difference in % vs placebo (95% CI) p-value	31.2 (17.5, 43.6) <0.0001**		39.6 (24.6, 52.6) <0.0001**	
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%	23%	63%
ASAS Partial Remission	18%	33%*	19%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	SIMPONI 50 mg	Placebo	SIMPONI 50 mg
n ^c	87	74	69	61
Mean change in SPARCC ^d MRI sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

^a n reflects randomized and treated patients

^b Primary endpoint

^c n reflects number of patients with baseline and week 16 MRI data

^d SPARCC (Spondyloarthritis Research Consortium of Canada)

** p < 0.0001 for Simponi vs placebo comparisons

* p < 0.05 for Simponi vs placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with Simponi 50 mg compared to placebo at week 16 (Table 8). Improvements were observed at the first assessment (week 4) after the initial Simponi administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with Simponi 50 mg compared to placebo (Table 8). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also

showed improvement from baseline to week 16 in patients treated with Simponi 50 mg compared to placebo.

Improvements in spinal mobility as assessed by BASMI (Bath Ankylosing Spondylitis Metrology Index) and in physical function as assessed by the BASFI were demonstrated in Simponi 50 mg-treated patients as compared to placebo-treated patients. Patients treated with Simponi experienced more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced more improvements in productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI questionnaire than patients receiving placebo. The endpoints for work time missed and impairment while working, as assessed by the WPAI questionnaire, showed no evidence of difference between the golimumab and placebo groups.

For all of the endpoints described above, improvements were also demonstrated in the OSI population at week 16.

In both the AT and OSI populations, clinical responses were maintained through 52 weeks of therapy (which included 36 weeks open-label).

In the subset of patients who had both a negative MRI and a normal CRP at baseline, a benefit on treatment with SIMPONI was not observed.

There are no data on the effects of golimumab on disease progression or structural damage in nr- Axial SpA patients.

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. Stable treatment with oral 5-aminosalicylic acid, oral corticosteroids, 6-mercaptopurine or azathioprine or a history of failure to response to or tolerate at least one of those previous treatments or steroid dependency were also entry criteria. Subjects with severe extensive colitis, subjects with UC limited to the rectum or to <2 cm of colon and subjects who had ever received biologic therapy targeted at TNF α (e.g., infliximab, etanercept, certolizumab, adalimumab) were excluded. 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.

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 $\geq 30\%$ 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.

Table 9 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
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 $\geq 30\%$ 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, 38.9% (21/54) given SIMPONI 100 mg and 24.1% (13/54) given placebo maintained clinical remission at Weeks 30 and 54 (p=0.07398).

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).

Following SC administration in patients with nr-Axial SpA, antibodies to SIMPONI, all neutralizing *in vitro*, were detected in 7% of SIMPONI-treated patients through Week 52.

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.

INDICATIONS

Rheumatoid arthritis (RA)

SIMPONI, in combination with methotrexate, is indicated for:

The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate. SIMPONI has also been shown to inhibit the progression of joint damage as measured by X-ray.

Psoriatic arthritis (PsA)

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

The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. SIMPONI has also been shown to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease, and improve physical function.

Axial Spondyloarthritis

Ankylosing spondylitis (AS)

SIMPONI is indicated for:

The treatment of active ankylosing spondylitis in adult patients.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)

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

Ulcerative colitis (UC)

SIMPONI is indicated for:

The treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy. Patients should show a clinical response within 6 weeks of treatment to continue treatment beyond that time (see CLINICAL TRIALS)

CONTRAINDICATIONS

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see PRECAUTIONS).

Concurrent administration of SIMPONI with anakinra or abatacept (see PRECAUTIONS).

Moderate or severe heart failure (NYHA class III/IV) (see PRECAUTIONS).

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

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-blockers including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, legionellosis 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 CONTRAINDICATIONS and PRECAUTIONS, "Interactions with other medicines").

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 or travelled in 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 infections, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis. 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 Hepatitis B virus (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 and lymphoproliferative disorders

The potential role of TNF-blocking therapy in the development of malignancies is not known. Based on the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded. 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 \leq 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 of hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Leukaemia

Cases of acute and chronic leukaemia have been reported with post-marketing 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 ADVERSE EFFECTS). 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 has been reported in patients treated with TNF blocking agents, including SIMPONI. Merkel cell carcinoma has been reported in patients treated with other TNF-blocking agents (see ADVERSE EFFECTS). 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 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.

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 ADVERSE EFFECTS, “Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies”).

Haematological cytopaenias

There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers. Cytopaenias including pancytopenia, 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 neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, 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 CONTRAINDICATIONS and PRECAUTIONS, “Interactions with other medicines”).

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 CONTRAINDICATIONS and PRECAUTIONS, “Interactions with other medicines”).

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 Vaccine / 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 systemic 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.

Use in children and adolescents

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

Use in the 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. There were no patients aged 47 and over in the nr-Axial SpA study.

Renal and hepatic insufficiency

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

Effects on ability to drive and use machines

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

Use in Pregnancy (Category C)

The use of SIMPONI in pregnant women is not recommended. 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. Studies in cynomolgus monkeys have shown no untoward effects on the course of pregnancy, embryofetal 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 PRECAUTIONS, Vaccinations and PRECAUTIONS, Interactions with other medicines).

Use in lactation

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.

Genotoxicity

No genotoxicity tests have been conducted with golimumab.

Carcinogenicity

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

Effects on fertility

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

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed. For the effect of immunomodulators on golimumab in UC, see PHARMACOLOGY, "Pharmacokinetics"

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, use of SIMPONI with abatacept or anakinra is not recommended (see CONTRAINDICATIONS and PRECAUTIONS). 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 PRECAUTIONS). Therapeutic infectious agents should not be given concurrently with SIMPONI (see PRECAUTIONS).

Methotrexate

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 PHARMACOLOGY, "Pharmacokinetics").

ADVERSE EFFECTS

Safety data from Phase 2 and 3 clinical trials are available from 5519 SIMPONI-treated patients including 3090 with RA, 394 with PsA, 564 with AS, 1240 with UC and 231 with severe persistent asthma.

Table 10 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 through Week 16 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 10: 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%)
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%)

	Placebo ± DMARDs N=639	SIMPONI ± DMARDs N=1659
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).		

Table 11 summarises adverse drug reactions observed in Phase 2/3 clinical studies from the SIMPONI-treated patients with RA, PsA, AS, UC, and severe persistent asthma. Within the designated system organ classes, the adverse reactions are listed under headings of frequency, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 11 Tabulated List of Adverse Drug Reactions

<p>Infections and infestations</p> <p>Very common: Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)</p> <p>Common: Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess</p> <p>Uncommon: Sepsis including septic shock, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), bacterial arthritis, pyelonephritis</p> <p>Rare: Hepatitis B reactivation, tuberculosis, infective bursitis</p>
<p>Neoplasms, benign, malignant and unspecified</p> <p>Uncommon: Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)</p> <p>Rare: Lymphoma, leukaemia</p> <p>Not known: Paediatric malignancy*</p>
<p>Investigations</p> <p>Uncommon: Neutrophil count decreased</p>
<p>Blood and lymphatic system disorders</p> <p>Common: Anaemia</p> <p>Uncommon: Leucopaenia, thrombocytopaenia, pancytopaenia</p> <p>Rare: Aplastic anaemia</p>
<p>Immune system disorders</p> <p>Common: Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive</p> <p>Rare: Vasculitis (systemic)</p>
<p>Endocrine disorders</p> <p>Uncommon: Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)</p>
<p>Metabolism and nutrition disorders</p> <p>Uncommon: Blood glucose increased, lipids increased</p>
<p>Psychiatric disorders</p> <p>Common: Depression, insomnia</p>
<p>Nervous system disorders</p> <p>Common: Dizziness, headache, paraesthesia</p> <p>Uncommon: Balance disorders</p> <p>Rare: Demyelinating disorders (central and peripheral), dysguesia</p>
<p>Eye disorders</p> <p>Uncommon: Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritis and irritation)</p>
<p>Cardiac disorders</p> <p>Uncommon: Arrhythmia, ischemic coronary artery disorders</p> <p>Rare: Congestive heart failure (new onset or worsening)</p>

Table 11 Tabulated List of Adverse Drug Reactions

Vascular disorders	Common: Hypertension Uncommon: Thrombosis (such as deep venous and aortic), flushing Rare: Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Common: Asthma and related symptoms (such as wheezing and bronchial hyperactivity) Uncommon: Interstitial lung disease
Gastrointestinal disorders	Common: Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis Uncommon: Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders	Common: Alanine aminotransferase increased, aspartate aminotransferase increased Uncommon: Cholelithiasis, hepatic disorders
Skin and subcutaneous tissue disorders	Common: Pruritus, rash, alopecia, dermatitis Uncommon: Psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria Rare: Vasculitis (cutaneous)
Musculoskeletal and connective tissue disorders	Rare: Lupus-like syndrome
Renal and urinary disorders	Rare: Bladder disorders, renal disorders
Reproductive system and breast disorders	Uncommon: Breast disorders, menstrual disorders
General disorders and administration site conditions	Common: Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), chest discomfort Rare: Impaired healing
Injury, poisoning and procedural complications	Common: Bone fractures

*: Observed with other TNF-blocking agents, but not observed in clinical studies with golimumab.

Infections (see PRECAUTIONS)

Upper respiratory tract infection was the most common adverse reaction reported in the combined controlled Phase 3 RA, PsA and AS studies through Week 16 and the controlled Phase 2/3 induction studies in UC through Week 6, occurring in 12.6% of SIMPONI-treated patients (incidence per patient-year: 0.61; 95% CI: 0.55, 0.67) as compared with 10.7% of control patients (incidence per patient-year: 0.53; 95% CI: 0.44, 0.63). In controlled and uncontrolled portions of the studies with a median follow-

up of approximately 2 years, the incidence per patient year of upper respiratory tract infections was 0.36 events; 95% CI: 0.35, 0.37, for SIMPONI-treated patients.

In the combined controlled Phase 3 RA, PsA and AS studies through Week 16 and the controlled Phase 2/3 induction studies in UC through Week 6 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 2 years, the incidence per patient year of infections was 0.84 events; 95% CI: 0.82, 0.85 for SIMPONI treated patients.

Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, invasive fungal infections and other opportunistic infections and tuberculosis. Some of these infections have been fatal. In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI-treated and 1.3% of control-treated patients. Through Week 16, the incidence of serious infections per patient-year of follow-up was 0.07; 95% CI: 0.05, 0.11 for the SIMPONI 100 mg group, 0.03; 95% CI: 0.01, 0.07 for the SIMPONI 50 mg group and 0.04; 95% CI: 0.02, 0.08 for the placebo group. In controlled Phase 2/3 trials through Week 6 of SIMPONI induction in UC, 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, and AS with a median follow-up of approximately 2 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.

The incidence per 100 patient-years of TB in patients receiving SIMPONI induction and 100 mg during the maintenance portion of the UC study was 0.52; 95% CI: 0.11, 1.53.

Malignancies (see PRECAUTIONS)

Lymphoma

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

In the controlled and uncontrolled portions of these trials with a median follow-up of approximately 2 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, 0.23) and 0.15 (0.05, 0.32) 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 combined placebo -controlled periods of the SIMPONI Phase 2 and Phase 3 clinical trials in RA, PsA and AS of the Phase 3 RA, PsA and AS studies (through Week

24 in GO-FORWARD, GO-AFTER, GO-REVEAL and GO-RAISE, and through Week 52 in GO-BEFORE) and placebo-controlled Phase 2/3 induction studies in UC (through Week 6), the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the SIMPONI and the control groups. Through a median follow-up of approximately 2 years, 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 rheumatologic indications, 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 PRECAUTIONS)

In the controlled and uncontrolled periods of the Phase 3 RA, PsA and AS studies and Phase 2/3 UC studies with a median follow-up of approximately 2 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. In controlled and uncontrolled portions of the Phase 2/3 studies in UC with a mean follow-up of approximately 1 year, there was one case of demyelination observed with SIMPONI.

Liver enzyme elevations

In the pivotal trials in RA, PsA and AS, 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 controlled Phase 3 trials through Week 16, Phase 3 trials through Week 16, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of SIMPONI and control patients in the RA and PsA studies (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 controlled Phase 2/3 trials through Week 6 of SIMPONI induction in UC, 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 1 year, the incidence of mild ALT elevations was 17.4% in patients receiving SIMPONI.

In the RA and AS studies through Week 16, ALT elevations ≥ 5 x ULN were uncommon and seen in more SIMPONI-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was similar in both SIMPONI-treated and control patients. The majority of these elevations were asymptomatic.

In controlled Phase 2/3 trials through Week 6 of SIMPONI induction in UC, 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 1 year, the incidence of ALT elevations ≥ 5 x ULN was 0.7% 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 combined controlled Phase 3 RA, PsA and AS trials through Week 16 and a controlled Phase 2/3 induction trial in UC through Week 6, 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

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

In the controlled and uncontrolled periods of the Phase 3 RA, PsA and AS studies and Phase 2/3 UC studies through 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 with anti-dsDNA negative at baseline was 1.1%.

Patients with non-radiographic axial spondyloarthritis

The safety observed in adult patients with nr-AxSpA was similar to that seen in previous clinical trials of golimumab in adult patients.

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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$), very rare ($< 1/10,000$, including isolated reports).

System Organ Class	Adverse Drug Reaction	Frequency
Neoplasm Benign and Malignant	Melanoma Merckel cell carcinoma, hepatosplenic T-cell lymphoma	Rare Unknown*
Immune System Disorders	Serious systemic hypersensitivity reactions (including anaphylactic reaction) Sarcoidosis	Rare Rare
Skin and Subcutaneous Tissue Disorders	Bullous skin reactions Skin exfoliation	Uncommon Rare

* Observed with other TNF-blocking agents

DOSAGE AND 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, non-radiographic axial spondyloarthritis 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.

Non-radiographic axial spondyloarthritis

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

Available data in non-radiographic axial spondyloarthritis suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

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.

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.

Instructions for administration and disposal

Prior to administration, visually inspect the solution for particles and discolouration through the viewing window. SIMPONI should be clear to slightly opalescent and colourless to light yellow. The solution should not be used if discoloured, or cloudy, or if foreign particles are present.

The needle cover on the pre-filled syringe as well as the pre-filled syringe in the pre-filled pen, contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex (see PRECAUTIONS).

At the time of dosing, if multiple injections are required, the injections should be administered at different sites on the body. Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

Comprehensive instructions for the administration of SIMPONI are given in the Patient Instruction Leaflet. This product is for single use in one patient only. Patients should be instructed to inject the full amount of SIMPONI according to the directions provided in the Patient Instruction Leaflet. Discard any residue; any unused product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, SIMPONI must not be mixed with other medicinal products. SIMPONI contains no antimicrobial agent.

OVERDOSAGE

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.

Contact the Poisons Information Centre on 131126 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

SIMPONI 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 PRECAUTIONS, "Allergic reactions"). SIMPONI is available in two strengths: 50 mg of golimumab in 0.5 mL and 100 mg of golimumab in 1 mL. SIMPONI is available in packs of 1 or 3* pre-filled syringe(s).

SIMPONI SmartJect injector 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 PRECAUTIONS, "Allergic reactions"). SIMPONI is available in two strengths: 50 mg of golimumab in 0.5 mL and 100 mg of golimumab in 1 mL. SIMPONI is available in packs of 1 or 3* pre-filled pen(s).

* Not currently supplied in Australia.

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.

NAME AND ADDRESS OF SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Road
Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

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POISON SCHEDULE OF MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

13 November 2009

DATE OF MOST RECENT AMENDMENT

2 September 2016