SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Simponi 45 mg/0.45 mL solution for injection in pre-filled pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled pen contains 45 mg golimumab* in 0.45 mL. 1 mL solution contains 100 mg golimumab.

Each pre-filled pen can deliver 0.1 mL to 0.45 mL (corresponding to 10 mg to 45 mg golimumab) in increments of 0.05 mL.

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

Excipient with known effect

Each pre-filled pen contains 18.45 mg sorbitol (E420) per 45 mg dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Simponi in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Simponi is indicated.

Patients treated with Simponi should be given the Patient Reminder Card which is included in the pack.

Posology

The 45 mg/0.45 mL pre-filled pen is for paediatric patients. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

Paediatric population

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis in children with body weight less than 40 kg

The recommended dose of Simponi for children with a body weight less than 40 kg with polyarticular juvenile idiopathic arthritis is 30 mg/m^2 body surface area up to maximum single dose of 40 mg administered once a month, on the same date each month. The prescribed volume of injection should be selected according to patient's height and weight as shown in Table 1.

Table 1: Simponi dose in millilitres (mL) by height and weight of patients with pJIA

		Total Body Weight (kg)						
		10-12	**13-17**	**18-22**	**23-27**	**28-32**	**33-37**	**38-39**
		Dose (mL)						
Height (cm)	**70 to < 75**	0.15	0.15	0.2				
	75 to < 85	0.15	0.15	0.2	0.2			
	85 to < 95	0.15	0.2	0.2	0.25	0.25	0.3	
	95 to < 105	0.15	0.2	0.2	0.25	0.25	0.3	0.3
	105 to < 115	0.15	0.2	0.25	0.25	0.3	0.3	0.3
	115 to < 125	0.2	0.2	0.25	0.25	0.3	0.3	0.35
	125 to < 135		0.2	0.25	0.3	0.3	0.35	0.35
	135 to < 145		0.25	0.25	0.3	0.3	0.35	0.35
	145 to < 155			0.25	0.3	0.35	0.35	0.4
	155 to < 165			0.3	0.3	0.35	0.35	0.4
	165 to < 175				0.35	0.35	0.4	0.4
	175 to < 180					0.35	0.4	0.4

Polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg

For children with body weight of at least 40 kg, a 50 mg pre-filled pen or pre-filled syringe is available. For the posology of the 50 mg dosing regimen, see section 4.2 of the Simponi 50 mg pre-filled pen or pre-filled syringe SmPC.

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

There is no relevant use of Simponi in patients aged less than 2 years for the indication of pJIA.

Missed dose

If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:
if the dose is less than 2 weeks late, the patient should inject the forgotten dose and stay on the original schedule.
if the dose is more than 2 weeks late, the patient should inject the forgotten dose and a new schedule should be established from the date of this injection.

Special populations

Renal and hepatic impairment

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

Paediatric population

The safety and efficacy of golimumab have not been established in patients with pJIA below the age of 2 years. No data are available.

Method of administration

Simponi is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the prescribed amount of Simponi according to the comprehensive instructions for use provided in the pack.
For administration instructions, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with golimumab. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with golimumab must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Golimumab should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of golimumab in patients with a chronic infection or a history of recurrent infection. Patients should be advised of, and avoid exposure to, potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.
Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive

fungal and opportunistic infections, including fatalities, have been reported in patients receiving golimumab. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with golimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of golimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of golimumab treatment should be carefully considered before initiation of golimumab therapy. In at-risk patients treated with golimumab, an invasive fungal infection should be suspected if they develop a serious systemic illness. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections, if feasible.

Tuberculosis

There have been reports of tuberculosis in patients receiving golimumab. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with golimumab, all patients must be evaluated for both active and inactive (‘latent’) tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin or blood test and chest X-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the Patient Reminder Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, golimumab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of golimumab therapy should be very carefully considered.

If inactive (‘latent’) tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of golimumab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of golimumab. Use of anti-tuberculosis therapy should also be considered before the initiation of golimumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Cases of active tuberculosis have occurred in patients treated with golimumab during and after treatment for latent tuberculosis. Patients receiving golimumab should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after golimumab treatment.

Hepatitis B virus reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including golimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with golimumab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with golimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, golimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

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

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤ 18 years of age) in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.

Lymphoma and leukaemia

In the controlled portions of clinical trials of all the TNF-blocking agents including golimumab, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), the incidence of lymphoma in golimumab-treated patients was higher than expected in the general population. Cases of leukaemia have been reported in patients treated with golimumab. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see section 4.8). This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of cases have occurred in adolescent and young adult males with nearly all on concomitant treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) for inflammatory bowel disease. The potential risk with the combination of AZA

or 6-MP and golimumab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Malignancies other than lymphoma

In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, AS, and ulcerative colitis (UC), the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups.

Colon dysplasia/carcinoma

It is not known if golimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with golimumab, the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

In an exploratory clinical trial evaluating the use of golimumab in patients with severe persistent asthma, more malignancies were reported in patients treated with golimumab compared with control patients (see section 4.8). The significance of this finding is unknown.

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

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including golimumab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including golimumab. Some cases had a fatal outcome. In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Golimumab has not been studied in patients with CHF. Golimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and golimumab must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events

Use of TNF-blocking agents, including golimumab, 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 and peripheral demyelinating disorders. In patients with pre-existing or recent onset of

demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of golimumab therapy. Discontinuation of golimumab should be considered if these disorders develop (see section 4.8).

Surgery

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

Immunosuppression

The possibility exists for TNF-blocking agents, including golimumab, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes

The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with golimumab and is positive for antibodies against double-stranded DNA, treatment with golimumab should be discontinued (see section 4.8).

Haematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis, aplastic anaemia, and thrombocytopenia in patients receiving TNF-blockers, including golimumab. 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 golimumab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of golimumab and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of golimumab and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of golimumab with other biological therapeutics used to treat the same conditions as golimumab. The concomitant use of golimumab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological disease modifying anti-rheumatic drugs (DMARDs)

Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations/therapeutic infectious agents

Patients treated with golimumab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). 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 golimumab.

Allergic reactions

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

Latex sensitivity

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

Special populations

Elderly (≥ 65 years)

In the Phase III studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received golimumab were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections. There were no patients age 45 and over in the non-radiographic axial spondyloarthritis (nr-Axial SpA) study.

Renal and hepatic impairment

Specific studies of golimumab have not been conducted in patients with renal or hepatic impairment. Golimumab should be used with caution in subjects with impaired hepatic function (see section 4.2).

Paediatrics

Vaccinations

If possible, it is recommended that prior to initiating golimumab therapy, paediatric patients be brought up to date with all immunisations in agreement with current immunisation guidelines (see Vaccinations/ therapeutic infectious agents above).

Excipients

Simponi contains sorbitol (E420). In patients with rare hereditary problems of fructose intolerance, the additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account (see section 2).

Potential for medication errors

It is important that the correct dose is administered as indicated in the posology (see section 4.2). Care should be taken to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics

The combination of golimumab with other biological therapeutics used to treat the same conditions as golimumab, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines/therapeutic infectious agents

Live vaccines should not be given concurrently with golimumab (see sections 4.4 and 4.6).

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

Methotrexate

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There is a moderate amount (approximately 400) of prospectively collected pregnancies exposed to golimumab resulting in live birth with known outcomes, including 220 pregnancies exposed during the first trimester. In a population-based study from Northern Europe including 131 pregnancies (and 134 infants), there were 6/134 (4.5%) events of major congenital anomalies following *in utero* exposure to Simponi vs 599/10,823 (5.5%) events for non-biologic systemic therapy compared to 4.6% in the general population of the study. Confounder-adjusted odds ratios were OR 0.79 (95% CI 0.35-1.81) for Simponi vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for Simponi vs. the general population, respectively.

Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The available clinical experience is limited. Golimumab should only be used during pregnancy if clearly needed.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding

It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

Fertility

No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Simponi has minor influence on the ability to ride bicycles, drive and use machines. Dizziness may however occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12.6% of golimumab-treated patients compared with 11.0% of control patients. The most serious ARs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions

ARs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed in Table 1. Within the designated system organ classes, the ARs are listed under headings of frequency and using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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 1
Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
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
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma, Merkel cell carcinoma
Not known:	Hepatosplenic T-cell lymphoma*, Kaposi's sarcoma
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anaemia
Uncommon:	Thrombocytopenia, pancytopenia
Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	
Common:	Dizziness, headache, paraesthesia
Uncommon:	Balance disorders
Rare:	Demyelinating disorders (central and peripheral), dysgeusia

Eye disorders	
Uncommon:	Visual disorders (such as blurred vision and decreased visual acuity), conjunctivitis, eye allergy (such as pruritis and irritation)
Cardiac disorders	
Uncommon:	Arrhythmia, ischemic coronary artery disorders
Rare:	Congestive heart failure (new onset or worsening)
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:	Bullous skin reactions, psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
Rare:	Lichenoid reactions, skin exfoliation, vasculitis (cutaneous)
Not known:	Worsening of symptoms of dermatomyositis
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.

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

Description of selected adverse reactions

Infections

In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per 100 subject-years: 60.8; 95% CI: 55.0, 67.1) compared with 11.0% of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34.9 events; 95% CI: 33.8, 36.0 for golimumab treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20.2% of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81.1 events; 95% CI: 79.5, 82.8 for golimumab treated patients.

In the controlled period of RA, PsA, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-treated patients compared with 1.5% of control-treated patients. Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. In the controlled and uncontrolled portions of the pivotal trials with a median follow-up of up to 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg.

Malignancies

Lymphoma

The incidence of lymphoma in golimumab-treated patients during the pivotal trials was higher than expected in the general population. In the controlled and uncontrolled portions of these trials with a median follow-up of up to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 11 subjects (1 in the golimumab 50 mg treatment groups and 10 in the golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.03 (0.00, 0.15) and 0.13 (0.06, 0.24) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.57) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease (see section 4.4).

Malignancies other than lymphoma

In the controlled periods of pivotal trials and through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar to the general population.

In the controlled and uncontrolled periods of pivotal trials with a median follow-up of up to 3 years, non-melanoma skin cancer was diagnosed in 5 placebo-treated, 10 golimumab 50 mg-treated and 31 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.36 (0.26, 0.49) for combined golimumab and 0.87 (0.28, 2.04) for placebo.

In the controlled and uncontrolled period of pivotal trials with a median follow-up of up to 3 years, malignancies besides melanoma, non-melanoma skin cancer and lymphoma were diagnosed in 5 placebo-treated, 21 golimumab 50 mg-treated and 34 golimumab 100 mg-treated subjects with an incidence (95% CI) per 100 subject-years of follow-up of 0.48 (0.36, 0.62) for combined golimumab and 0.87 (0.28, 2.04) for placebo (see section 4.4).

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 in the combined golimumab treatment group (n = 230) and none in the placebo treatment group (n = 79) were reported. 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.

Neurological events

In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg (see section 4.4).

Liver enzyme elevations

In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-treated patients (26.9%) than control patients (10.6%) 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 golimumab-treated and control patients in RA and PsA studies. In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (8.0% to 6.9%, respectively). In controlled and uncontrolled periods of the UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients with mild ALT elevations was 24.7% in patients receiving golimumab during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-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 golimumab-treated and control patients. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medicinal products. No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year). In the controlled periods of the pivotal UC trials, of golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-treated patients compared to placebo-treated patients (0.3% to 1.0%, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0.8% in patients receiving golimumab during the maintenance portion of the UC study.

Within the RA, PsA, AS, and nr-Axial SpA pivotal trials, one patient in an RA trial with pre-existing liver abnormalities and confounding medicinal products treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions

In the controlled periods of pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control patients. The presence of antibodies to golimumab may increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled Phase IIb and/or III trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase II/III trials in UC, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies

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

Paediatric population

Polyarticular juvenile idiopathic arthritis

The safety of golimumab has been studied in a phase III study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors.

Pharmacodynamic effects

The binding of human TNF by golimumab was shown to neutralise TNF-α-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. *In vitro*, 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.

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 (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 maintained through week 24.

Clinical efficacy

Polyarticular juvenile idiopathic arthritis
The safety and efficacy of Simponi was evaluated in a randomised, double-blind, placebo-controlled, withdrawal study (GO-KIDS) in 173 children (2 to 17 years of age) with active pJIA with at least 5 active joints and an inadequate response to MTX. Children with polyarticular course JIA (rheumatoid factor positive or negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis or systemic JIA with no current systemic symptoms) were included in the study. The baseline median number of active joints was 12, and median CRP was 0.17 mg/dL.

Part 1 of the study consisted of a 16-week open-label phase in which 173 enrolled children received Simponi 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks and MTX. The 154 children who achieved an American College of Rheumatology (ACR) Ped 30 response at week 16 entered Part 2 of the study, the randomised withdrawal phase, and received Simponi 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX every 4 weeks. After disease flare, children received Simponi 30 mg/m^2 (maximum 50 mg) + MTX. At week 48, children entered a long-term extension.

Children in this study demonstrated ACR Ped 30, 50, 70, and 90 responses from week 4.

At week 16, 87% of children were ACR Ped 30 responders, and 79%, 66%, and 36% of children were ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively. At week 16, 34% of children had inactive disease defined as having the presence of all of the following: no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR (< 20 mm/hour) or CRP (< 1.0 mg/dL); physician global assessment of disease activity (≤ 5 mm on the VAS); duration of morning stiffness < 15 minutes.

At week 16, all ACR Ped components demonstrated clinically relevant improvement from baseline (see Table 3).

Table 3
Improvements from baseline in ACR Ped components at week 16[a]

	Median percent improvement
	Simponi 30 mg/m^2 n[b] = 173
Physicians global assessment of disease (VAS[c] 0-10 cm)	88%
Subject/parent global assessment of overall well-being (VAS 0-10 cm)	67%
Number of active joints	92%
Number of joints with limited range of motion	80%
Physical function by CHAQ[d]	50%
ESR (mm/h)[e]	33%

[a] baseline = week 0
[b] "n" reflects enrolled patients
[c] VAS: Visual Analogue Scale
[d] CHAQ: Child Health Assessment Questionnaire
[e] ESR (mm/h): erythrocyte sedimentation rate (millimetres per hour)

The primary endpoint, the proportion of children who were ACR Ped 30 responders at week 16 and who did not experience a flare between week 16 and week 48, was not achieved. The majority of children did not experience a flare between week 16 and week 48 (59% in the Simponi + MTX and 53% in the placebo + MTX groups, respectively; p = 0.41).

Pre-specified subgroup analyses of the primary endpoint by baseline CRP (≥ 1 mg/dL vs < 1 mg/dL) demonstrated higher flare rates in placebo + MTX vs Simponi + MTX treated subjects among subjects with baseline CRP ≥ 1 mg/dL (87% vs 40% p = 0.0068).

At week 48, 53% and 55% of children in the Simponi + MTX group and placebo + MTX group, respectively, were ACR Ped 30 responders, and 40% and 28% of children in the Simponi + MTX group and placebo + MTX group, respectively, achieved inactive disease.

Adult rheumatoid arthritis
The efficacy of Simponi was demonstrated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 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 or placebo were subcutaneously administered every 4 weeks.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

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

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX, through week 104 in GO-FORWARD and GO-BEFORE and through week 24 in GO-AFTER. In each

of the RA studies by study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms

Key ACR results for the Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 4 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 4
Key efficacy outcomes from the controlled portions of 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%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
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%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.

* $p \leq 0.001$

NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 (p = 0.053). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 4). Additional analyses were performed in subsets representative of the indicated

population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 responses were similar from week 104 through week 256.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response were observed from week 104 through week 256.

Radiographic response

In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 5.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group ($p = 0.003$). The radiographic effects observed at week 52 were maintained through week 104. Among patients remaining in the study and treated with Simponi, radiographic effects were similar from week 104 through week 256.

Table 5
Radiographic mean (SD) changes from baseline in total vdH-S score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n[a]	**160**	**159**
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	0.7 (2.8)	0.5 (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

* $p = 0.015$

** $p = 0.044$

Physical function and health-related quality of life

Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ DI. In these studies, Simponi demonstrated

clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ DI was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement in HAQ DI was similar from week 104 through week 256.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. Among patients remaining in the study and treated with Simponi, improvement of the SF-36 physical component was similar from week 104 through week 256. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Adult 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 and had at least mild psoriatic disease. 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%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or Simponi 100 mg. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). 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.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens through week 104. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg Simponi doses at the discretion of the study physician.

Signs and symptoms
Key results for the 50 mg dose at weeks 14 and 24 are shown in Table 6 and described below.

Table 6
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9%**	**51%**
Week 24	12%	52%
ACR 50		
Week 14	2%	30%
Week 24	4%	32%

ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* $p < 0.05$ for all comparisons;

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

[b] *Psoriasis Area and Severity Index*

[c] Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes 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. Among patients remaining in the study and treated with Simponi, similar rates of ACR 20/50/70 response was observed from week 104 through week 256.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

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. 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, DAS28 and HAQ DI responses were maintained through week 104. Among patients remaining in the study and treated with Simponi, DAS28 and HAQ DI responses were similar from week 104 through week 256.

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean ± SD score was 0.27 ± 1.3 in the placebo group compared with -0.16 ± 1.3 in the Simponi group; $p = 0.011$). Out of 146 patients who were randomised to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline. Among patients remaining in the study and treated with Simponi, similar rates of patients showed no progression from baseline from week 104 through week 256.

Immunogenicity

Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected by the enzyme immunoassay (EIA) method in 5% (105/2062) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. 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 golimumab without MTX (approximately 3% [41/1235] versus 8% [64/827], respectively).

In nr-Axial SpA, antibodies to golimumab were detected in 7% (14/193) of golimumab treated patients through week 52 by the EIA method.

In the Phase II and III UC studies through week 54, antibodies to golimumab were detected by the EIA method in 3% (26/946) of golimumab treated patients. Sixty-eight percent (21/31) of antibody-positive patients had neutralising antibodies *in vitro*. Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without immunomodulators (1% (4/308) versus 3% (22/638), respectively). Of patients that continued in the study extension and had evaluable samples through week 228, antibodies to golimumab were detected in 4% (23/604) of golimumab treated patients. Eighty-two percent (18/22) of antibody-positive patients had neutralising antibodies *in vitro*.

A drug-tolerant EIA method was used in the pJIA study for the detection of antibodies to golimumab. Due to the higher sensitivity and the improved drug tolerance, a higher incidence of antibodies to golimumab was expected to be detected with the drug-tolerant EIA method compared to the EIA method. In the Phase III pJIA study through week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% (69/172) of golimumab treated children of which a majority had a titre lower than 1:1000. An effect on serum golimumab concentrations was seen at titres of > 1:100 while an effect on efficacy was not seen until titres of > 1:1000, though the numbers of children with titres of > 1:1000 were low (N = 8). Among the children who tested positive for antibodies to golimumab, 39% (25/65) had neutralising antibodies. The higher incidence of antibodies with the drug-tolerant EIA method, because they were mainly low titre antibodies, did not have an apparent impact on drug levels, efficacy and safety and therefore does not represent any new safety signal.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.4). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

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

5.2 Pharmacokinetic properties

Absorption

Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 µg/mL.

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

Distribution

Following a single IV administration, the mean volume of distribution was 115 ± 19 mL/kg.

Elimination

The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

When 50 mg golimumab was administered subcutaneously 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 golimumab subcutaneously every 4 weeks resulted in a mean (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/mL in patients with active PsA and approximately 0.8 ± 0.4 μg/mL in patients with AS. Steady-state trough mean 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.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/mL and 1.8 ± 1.1 μg/mL, respectively.

In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

Patients who developed antibodies to golimumab generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

Linearity

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

Effect of weight on pharmacokinetics

There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

Paediatric population

The pharmacokinetics of golimumab were determined in 173 children with pJIA with an age range from 2 to 17 years of age. In the pJIA study, children who received

golimumab 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks, had median steady-state trough golimumab concentrations which were similar across different age groups, and which were also similar to or slightly higher than those seen in adult RA patients who received 50 mg golimumab every 4 weeks.

Population pharmacokinetic/pharmacodynamic modelling and simulation in children with pJIA confirmed the relationship between golimumab serum exposures and clinical efficacy and supports the dosing regimen of golimumab 30 mg/m^2 every 4 weeks in children with pJIA.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)

Histidine

Histidine hydrochloride monohydrate

Polysorbate 80

Water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

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

Simponi may be stored at temperatures up to a maximum of 25°C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once Simponi has been stored at room temperature, it should not be returned to refrigerated storage. Simponi must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

Simponi 45 mg/0.45 mL solution for injection

0.45 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex) in a pre-filled pen. Each pre-filled pen can deliver 0.1 mL to 0.45 mL in increments of 0.05 mL.

Pack size of 1 pre-filled pen.

6.6 Special precautions for disposal

Simponi is supplied in a single use pre-filled pen called VarioJect. Each pack is provided with instructions for use that fully describe the use of the pen. After removing the pre-filled pen from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The pen should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Simponi in a pre-filled pen are included in the pack.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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