SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Gotenfia 50 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL pre-filled syringe contains 50 mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a Chinese hamster Ovary (CHO) cell line with recombinant DNA technology.

Excipient with known effect

Each ml contains 0.2 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)

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

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

Golimumab, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

Gotenfia in combination with 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.

Psoriatic arthritis (PsA)

Gotenfia, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Axial spondyloarthritis

Ankylosing spondylitis (AS)

Gotenfia is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)

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

Ulcerative colitis (UC)

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

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, or ulcerative colitis. Patients treated with Gotenfia should be given the Patient Card.

Posology

Rheumatoid arthritis

Gotenfia 50 mg given once a month, on the same date each month. Gotenfia should be given concomitantly with MTX.

Psoriatic arthritis, ankylosing spondylitis, or non-radiographic axial spondyloarthritis

Gotenfia 50 mg given once a month, on the same date each month.

For all of the above indications, 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 patients who show no evidence of therapeutic benefit within this time period.

Patients with body weight greater than 100 kg

For all of the above indications, in patients with RA, PsA, AS, or nr-Axial SpA with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Ulcerative colitis

Patients with body weight less than 80 kg

Gotenfia given as an initial dose of 200 mg, followed by 100 mg at week 2. Patients who have an adequate response should receive 50 mg at week 6 and every 4 weeks thereafter. Patients who have an inadequate response may benefit from continuing with 100 mg at week 6 and every 4 weeks thereafter (see section 5.1).

Patients with body weight greater than or equal to 80 kg

Gotenfia given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter (see section 5.1).

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

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

Missed dose

If a patient forgets to inject Gotenfia 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

Elderly (≥ 65 years)

No dose adjustment is required in the elderly.

Renal and hepatic impairment

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

Paediatric population

The safety and efficacy of golimumab in patients aged less than 18 for indications other than pJIA have not been established.

Polyarticular juvenile idiopathic arthritis

Gotenfia 50 mg administered once a month, on the same date each month, for children with a body weight of at least 40 kg.

The recommended dose of golimumab in children that weigh less than 40 kg is based on body weight. There is no dosage form for Gotenfia available for weight-based dosing in children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg. Thus, it is not possible to administer Gotenfia and another golimumab product should be used.

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.

Method of administration

Gotenfia 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 full amount of Gotenfia according to the comprehensive instructions for use provided in the package leaflet. If multiple injections are required, the injections should be administered at different sites on the body.

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 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 golimumab Phase IIb and Phase III clinical trials in RA, PsA and 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 golimumab Phase IIb and Phase III clinical trials in RA, PsA, AS, and 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 TNFα 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 DMARDs

Care should be taken and patients should continue to be monitored when switching from one biologic to another (different molecules or with different mechanisms of action), 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 syringe 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 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

This medicinal product contains 0.1 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.2 mg/ml. Polysorbates may cause allergic reactions.

Potential for medication errors

Gotenfia is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength 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 golimumab 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 golimumab vs. non-biologic systemic therapy and OR 0.95 (95% CI 0.42-2.16) for golimumab 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

Golimumab has minor influence on the ability to drive and use machines. Dizziness may however occur following administration of Gotenfia (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

MedDRA system organ class	**Frequency**	**Adverse Reaction**
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, pneumocystosis], 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.

MedDRA system organ class	**Frequency**	**Adverse Reaction**
	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, ischaemic 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, gastrooesophageal reflux disease.
Hepatobiliary disorders	Common:	Alanine aminotransferase increased, aspartate aminotransferase increased.
	Uncommon:	Cholelithiasis, hepatic disorders.

MedDRA system organ class	Frequency	Adverse Reaction
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 at: www.mhra.gov.uk/yellowcard 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

Gotenfia is a biosimilar medicinal product. Detailed information is available on the MHRA website https://www.gov.uk/government/organisations/medicines-and-healthcare-productsregulatory-agency.

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 golimumab 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 golimumab administration and were generally maintained through week 24.

Clinical efficacy

Rheumatoid arthritis

The efficacy of golimumab was demonstrated 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. golimumab 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, golimumab 50 mg + MTX, golimumab 100 mg + MTX or golimumab 100 mg + placebo. Patients receiving placebo + MTX were switched to golimumab 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, golimumab 50 mg, or golimumab 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, golimumab 50 mg + MTX, golimumab 100 mg + MTX or golimumab 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 golimumab 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 golimumab 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 golimumab 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 golimumab doses at the discretion of the study physician.

Signs and symptoms

Key ACR results for the golimumab 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 2 and are described below. Responses were observed at the first assessment (week 4) after the initial golimumab administration.

In GO-FORWARD, among 89 subjects randomised to golimumab 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 golimumab, 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 golimumab than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 2

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	Golimumab 50 mg + MTX	Placebo	Golimumab 50 mg	Placebo + MTX	Golimumab 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 golimumab 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 golimumab 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 2). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of golimumab 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 golimumab 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 golimumab, 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 golimumab 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 golimumab 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 golimumab, 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 golimumab 50 mg dose at week 52 are presented in Table 3.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the golimumab 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 golimumab, radiographic effects were similar from week 104 through week 256.

Table 3

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

	Placebo + MTX	**Golimumab 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, golimumab demonstrated clinically meaningful and statistically significant improvement in HAQ DI from baseline versus control at week 24. Among patients who remained on the golimumab 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 golimumab, 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 golimumab versus placebo at week 24. Among patients who remained on the golimumab 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 golimumab, 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).

Psoriatic arthritis

The safety and efficacy of golimumab 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. Golimumab or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, golimumab 50 mg, or golimumab 100 mg. Patients receiving placebo were switched to golimumab 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 golimumab 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 golimumab 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 4 and described below.

Table 4

Key efficacy outcomes from GO-REVEAL

	Placebo	Golimumab 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 golimumab 50 mg group.

Responses were observed at the first assessment (week 4) after the initial golimumab 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 golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomised to golimumab 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 golimumab, 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 golimumab-treated patients. Golimumab 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 golimumab 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 golimumab, 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.

Golimumab 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 golimumab group; $p = 0.011$). Out of

146 patients who were randomised to golimumab 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 golimumab, similar rates of patients showed no progression from baseline from week 104 through week 256.

Axial spondyloarthritis

Ankylosing spondylitis

The safety and efficacy of golimumab 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) ≥ 4 and a VAS for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Golimumab or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, golimumab 50 mg and golimumab 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in Table 5 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the golimumab 50 mg and 100 mg dosing regimens through week 24. By study design, patients in the long-term extension may have switched between the 50 mg and 100 mg golimumab doses at the discretion of the study physician.

Table 5

Key efficacy outcomes from GO-RAISE.

	Placebo	Golimumab 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%

* $p \leq 0.001$ for all comparisons

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

Among patients remaining in the study and treated with golimumab, the proportion of patients with an ASAS 20 and ASAS 40 response were similar from week 24 through week 256.

Statistically significant responses in BASDAI 50, 70 and 90 ($p \leq 0.017$) were also seen at weeks 14 and 24. Improvements in key measures of disease activity were observed at the first assessment (week 4) after the initial golimumab administration and were maintained through week 24. Among patients remaining in the study and treated with golimumab, similar rates of change from baseline in BASDAI were observed from week 24 through week 256. Consistent efficacy was seen in patients regardless of use of DMARDs (MTX, sulfasalazine and/or hydroxychloroquine), HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

Golimumab treatment resulted in significant improvements in physical function as assessed by changes from baseline in BASFI at weeks 14 and 24. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24. Among patients remaining in the study and treated with golimumab, improvements in physical function and health-related quality of life were similar from week 24 through week 256.

Non-radiographic axial spondyloarthritis

GO-AHEAD

The safety and efficacy of golimumab were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with severe 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 golimumab 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period in which all patients received golimumab 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 golimumab 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. The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 6 and described below.

Table 6

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	Golimumab 50 mg	Placebo	Golimumab 50 mg
n[a]	100	97	80	78
Responders, % of patients				
ASAS 20	40%	71%**	38%	77%**
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%**	23%	63%**
ASAS Partial Remission	18%	33%*	19%	35%*
ASDAS-C [b] < 1.3	13%	33%*	16%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	Golimumab 50 mg	Placebo	Golimumab 50 mg
nc	87	74	69	61
Mean change in SPARCC[d] MRI sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

a n reflects randomised and treated patients

b Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (AT-Placebo, N = 90; AT-golimumab 50 mg, N = 88; OSI-Placebo, N = 71; OSI-golimumab 50 mg, N = 71)

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

d SPARCC (Spondyloarthritis Research Consortium of Canada)

** $p < 0.0001$ for golimumab vs placebo comparisons

* $p < 0.05$ for golimumab vs placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with golimumab 50 mg compared to placebo at week 16 (Table 6). Improvements were observed at the first assessment (week 4) after the initial golimumab administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with golimumab 50 mg compared to placebo (Table 6). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also showed statistically significant improvement from baseline to week 16 in patients treated with golimumab 50 mg compared to placebo ($p < 0.0001$).

Statistically significant 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 golimumab 50 mg-treated patients as compared to placebo-treated patients ($p < 0.0001$). Patients treated with golimumab experienced

significantly more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced significantly 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.

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

In both the AT and OSI populations, the improvements in signs and symptoms, spinal mobility, physical function, quality of life, and productivity observed at week 16 among patients treated with golimumab 50 mg continued in those remaining in the study at week 52.

GO-BACK

The efficacy and safety of continued golimumab treatment (full or reduced dosing frequency) compared with treatment withdrawal was assessed in adult patients (18-45 years of age) with active nr-axSpA who demonstrated sustained remission during 10 months of monthly treatment with open-label golimumab (GO-BACK). Eligible patients (who achieved a clinical response by Month 4 and an inactive disease status (ASDAS < 1.3) at both Months 7 and 10) entering the double-blind withdrawal phase were randomised to continued monthly treatment with golimumab (full-treatment regimen, N = 63), every 2-month treatment with golimumab (reduced treatment regimen, N = 63) or monthly placebo treatment (treatment withdrawal, N = 62) for up to approximately 12 months.

The primary efficacy endpoint was the proportion of patients without a flare of disease activity. Patients who experienced a flare, i.e., had an ASDAS collected at 2 consecutive assessments that both showed either an absolute score of ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (end of open-label period), reinitiated monthly golimumab in an open-label retreatment phase to characterise clinical response.

Clinical response after double-blind treatment withdrawal

Among the 188 patients with inactive disease who received at least one dose of double-blind treatment, a significantly ($p < 0.001$) greater proportion of patients did not experience a disease flare when continuing golimumab with either the full-treatment (84.1%), or reduced treatment (68.3%) regimens compared with treatment withdrawal (33.9%) (Table 7).

Table 7

Analysis of the proportion of participants without a flare[a]

Full analysis set population (Period 2 – Double-blind)

Treatment	**n/N**	**%**	**Difference in % vs Placebo**

			Estimate (95% CI)[b]	p-Value[b]
GLM SC QMT	53/63	84.1	50.2 (34.1, 63.6)	< 0.001
GLM SC Q2MT	43/63	68.3	34.4 (17.0, 49.7)	< 0.001
Placebo	21/62	33.9		

Full Analysis Set includes all randomised participants who attained inactive disease in period 1 and received at least one dose of blinded study treatment.

a Defined as ASDAS at 2 consecutive visits that both show either absolute score ≥ 2.1 or post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23).

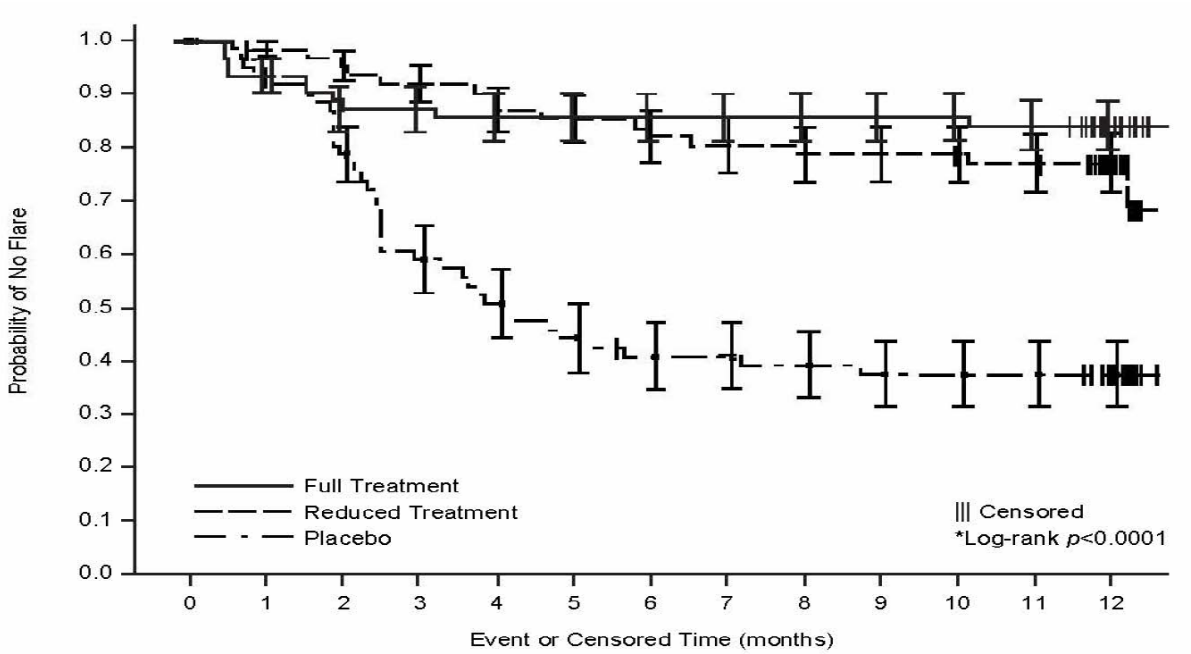
b Type I error rate over the multiple treatment comparisons (GLM SC QMT vs Placebo and GLM SC Q2MT vs Placebo) was controlled using a sequential (step-down) testing procedure. Derived based on the stratified Miettinen and Nurminen method with CRP level (> 6 mg/L or ≤ 6 mg/L) as stratification factor.

Participants who discontinued period 2 prematurely and prior to a 'flare' will be counted as having a 'flare'.

N = Total number of participants; n = number of participants without a flare; GLM = golimumab; SC = subcutaneous, QMT = monthly dosing; Q2MT = every other month dosing.

The difference in time-to-first flare between the treatment withdrawal group and either of the golimumab Treatment groups is shown in Figure 1 (log-rank $p < 0.0001$ for each comparison). In the placebo group, flares started approximately 2 months after golimumab was withdrawn, with the majority of flares occurring within 4 months of treatment withdrawal (Figure 1).

Figure 1: Kaplan-Meier Analysis of Time-to-First Flare



Participants at risk

GLM QMT	63	59	55	55	54	54	54	54	54	54	54	53	24
GLM Q2MT	63	61	58	56	53	52	50	49	48	48	46	45	19
PBO	62	57	48	36	31	27	24	24	23	22	22	22	10

*Endpoint not adjusted for multiplicity. Stratified by CRP level (> 6 mg/L or ≤ 6 mg/L). Flare was defined as an ASDAS at 2 consecutive visits that both showed either an absolute score of ≥ 2.1 or a post-withdrawal increase of ≥ 1.1 relative to Month 10 (Visit 23). Participants who did not flare were censored at the time of discontinuation or Month 13 of Period 2 double-blind treatment. Start of Period 2 represents Day 1 of the Kaplan-Meier analysis for the full analysis set.

Clinical response to retreatment for a disease flare

Clinical response was defined as a BASDAI improvement of ≥ 2 or ≥ 50% relative to the mean of the 2 consecutive BASDAI scores ascribed to the disease flare. Of the 53 participants in the reduced dosing or treatment withdrawal regimens who had a confirmed disease flare, 51 (96.2%) attained a clinical response to golimumab within the first 3 months of retreatment, although fewer patients (71.7%) were able to sustain it for all 3 months.

Ulcerative colitis

The efficacy of golimumab was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients.

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. In the dose confirming portion of the study, 761 patients were randomised to receive either 400 mg golimumab SC at week 0 and 200 mg at week 2 200 mg golimumab SC at week 0 and 100 mg at week 2, or placebo SC at weeks 0 and 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of golimumab through week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with golimumab. Patients were randomised to receive golimumab 50 mg, golimumab 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 golimumab through week 54 was assessed in this study. Patients who completed the maintenance study through week 54 continued treatment in a study-extension, with efficacy evaluated through week 216. Efficacy evaluation in the study extension was based on changes in corticosteroid use, Physician's Global Assessment (PGA) of disease activity, and improvement in quality of life as measured by Inflammatory Bowel Disease Questionnaire (IBDQ).

Table 8

Key efficacy outcomes from PURSUIT - Induction and PURSUIT - Maintenance

PURSUIT-Induction			
	Placebo N = 251	**Golimumab 200/100 mg** N = 253	
Percentage of patients			
Patients in clinical response at week 6[a]	30%	51%**	
Patients in clinical remission at week 6[b]	6%	18%**	
Patients with mucosal healing at week 6[c]	29%	42%*	
PURSUIT-Maintenance			
	Placebo[d] N = 154	**Golimumab 50 mg** N = 151	**Golimumab 100 mg** N = 151
Percentage of patients			
Maintenance of response (Patients in clinical response through week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both week 30 and week 54)[f]	16%	23%[g]	28%*

N = number of patients

** $p \leq 0.001$

* $p \leq 0.01$

a defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

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

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

d Golimumab induction only.

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.

g In patients weighing less than 80 kg, a greater proportion of patients who received 50 mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More golimumab-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both week 30 and week 54) in the 50 mg group (42%, nominal $p < 0.05$) and 100 mg group (42%, $p < 0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through week 54 and were not receiving concomitant corticosteroids at week 54 was greater in the 50 mg group (38%, 30/78) and 100 mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by week 54 was greater in the 50 mg group (41%, 32/78) and 100 mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid free was generally maintained through week 216.

Patients who did not achieve clinical response at week 6 in the PURSUIT-Induction studies were dosed golimumab 100 mg every 4 weeks in the PURSUIT-Maintenance study. At week 14, 28% of these patients achieved response defined by partial Mayo score (decreased by ≥ 3 points compared with start of induction). At week 54, the clinical outcomes observed in these patients were similar to the clinical outcomes reported for the patients achieving clinical response at week 6.

At week 6, golimumab significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who received golimumab maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through week 54.

Approximately 63% of patients who were receiving golimumab at the beginning of the study extension (week 56), remained on treatment through the end of the study (last golimumab administration at week 212).

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.

Paediatric population

Polyarticular juvenile idiopathic arthritis

The safety and efficacy of golimumab 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 golimumab 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks and MTX. The 154 children who achieved an ACR Ped 30 response at week 16 entered Part 2 of the study, the randomised withdrawal phase, and received golimumab 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX every 4 weeks. After disease flare, children received golimumab 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 9).

Table 9

Improvements from baseline in ACR Ped components at week 16a

	Median percent improvement
	Golimumab 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 golimumab + 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 golimumab + 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 golimumab + MTX group and placebo + MTX group, respectively, were ACR Ped 30 responders, and 40% and 28% of children in the golimumab + MTX group and placebo + MTX group, respectively, achieved inactive disease.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with the reference medicinal product containing golimumab in one or more subsets of the paediatric population in ulcerative colitis (see section 4.2 for information on paediatric use).

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 that the dosing regimen of golimumab 50 mg every 4 weeks in children with pJIA of at least 40 kg achieves similar exposures to those shown to be efficacious in adults.

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

L-histidine

L-histidine monohydrochloride monohydrate

trehalose

polysorbate 80 (E 433)

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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect it from light. Gotenfia may be stored at temperatures up to a maximum of 25 °C for a single period of up to 15 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 15 days from the date removed from the refrigerator).

Once Gotenfia has been stored at room temperature, it should not be returned to refrigerated storage. Gotenfia must be discarded if not used within the 15 days of room temperature storage.

6.5 Nature and contents of container

Gotenfia 50 mg solution for injection in pre-filled syringe

0.5 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex). Gotenfia is available in packs containing 1 pre-filled syringe and containing 3 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

The solution is clear to slightly opalescent, colourless to light yellow. Gotenfia should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

Comprehensive instructions for the preparation and administration of Gotenfia in a pre-filled syringe are given in the package leaflet.

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

7 MARKETING AUTHORISATION HOLDER

Internis Pharmaceuticals Ltd. (trading as STADA), Linthwaite, Huddersfield, HD7 5QH, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 40861/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2026

10 DATE OF REVISION OF THE TEXT

01/04/2026