Australian Government

Department of Health and Ageing

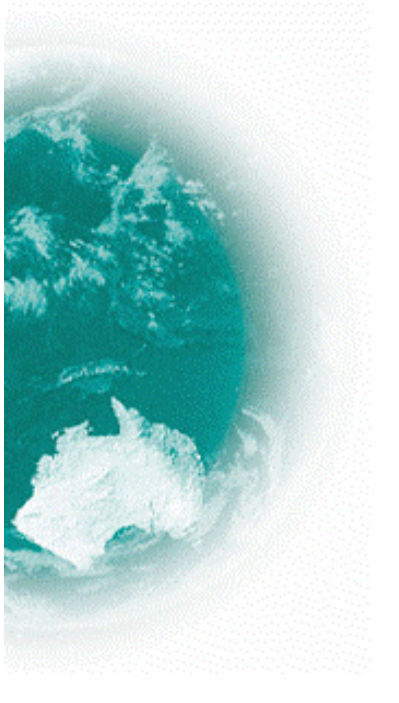
Therapeutic Goods Administration

Australian Public Assessment Report for Golimumab

Proprietary Product Name: Simponi

Submission No: PM-2008-1811-3

Sponsor: Schering-Plough Pty Ltd



December 2009

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New biological entity
Decision:	Approved
Active ingredient(s):	Golimumab
Product Name(s):	Simponi
Sponsor's Name and Address	Schering-Plough Pty Limited Level 4, 66 Waterloo Road North Ryde NSW 2113
Dose form(s):	Solution for Injection
Strength(s):	50mg/0.5 ml [Potency is expressed in terms of % bioactivity compared with the reference standard of the ability of the product to neutralize human TNF-α induced cytotoxicity]
Container(s):	Pre-filled 1ml syringe of type I borosilicate glass syringe barrel with a tetrafluoroethylene polymer coated gray butyl rubber plunger stopper. May be housed in a SmartJect auto-injector or UltraSafe Passive delivery device
Pack size(s):	1 box containing either 1 or 3 single use autoinjector pens 1 box containing 1 or 3 single use PFS
Approved Therapeutic use:	Rheumatoid arthritis (RA): Simponi, in combination with methotrexate, is indicated for the treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease modifying anti rheumatic drug (DMARD) therapy, including methotrexate, has been inadequate. Psoriatic arthritis (PsA): Simponi, alone or in combination with methotrexate, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug (DMARD) therapy has been inadequate. Simponi has also been shown to improve physical function. Ankylosing spondylitis (AS): Simponi is indicated for the treatment of active ankylosing spondylitis in adult patients.
Route(s) of administration:	Subcutaneous
Dosage:	50 mg given monthly on the same day every month

Product Background

Golimumab is a fully human immunoglobulin ($IgG1_k$) anti-TNF monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology. It forms high affinity, stable

complexes with both the soluble and transmembrane bioactive forms of human tumour necrosis factor (TNF), which prevents the binding of TNF to its receptors. Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis (RA), as well as spondyloarthropathies such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS), and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

This application was submitted in the CTD format with 7 volumes of modules 1-2 data, 14 volumes of module 3 biochemistry data, 30 volumes of module 4 non-clinical data and 97 volumes of module 5 clinical data. The indication was revised by the sponsor following the clinical evaluation report. There are two specific TGA adopted European guidelines relevant to this submission, besides the general guidelines.

CPMP/EWP/556/95 Rev 1, Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. Effective: 29 January 2007.

EMEA/CHMP/EWP/438/04: Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis. Effective: 5 February 2008

There is also a guideline adopted by the EMEA on ankylosing spondylitis (CPMP/EWP/4891/03) which has not been adopted by the TGA yet.

Regulatory Status at the Time of Submission

Golimumab has not been considered by the TGA previously, however other TNF inhibitors, including infliximab, have been previously considered.

The product has been approved in the USA and Canada. In the EU, a positive opinion was given by the CPMP in June 2009. A submission has also been lodged in New Zealand which is currently under evaluation.

Product Information

The approved product information current at the time this AusPAR was developed is contained at attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Golimumab, also named CNTO 148, is a recombinant human monoclonal antibody that selectively binds to human TNF. It is an IgG1 (gamma 1, kappa) antibody.

The golimumab molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide linkages.

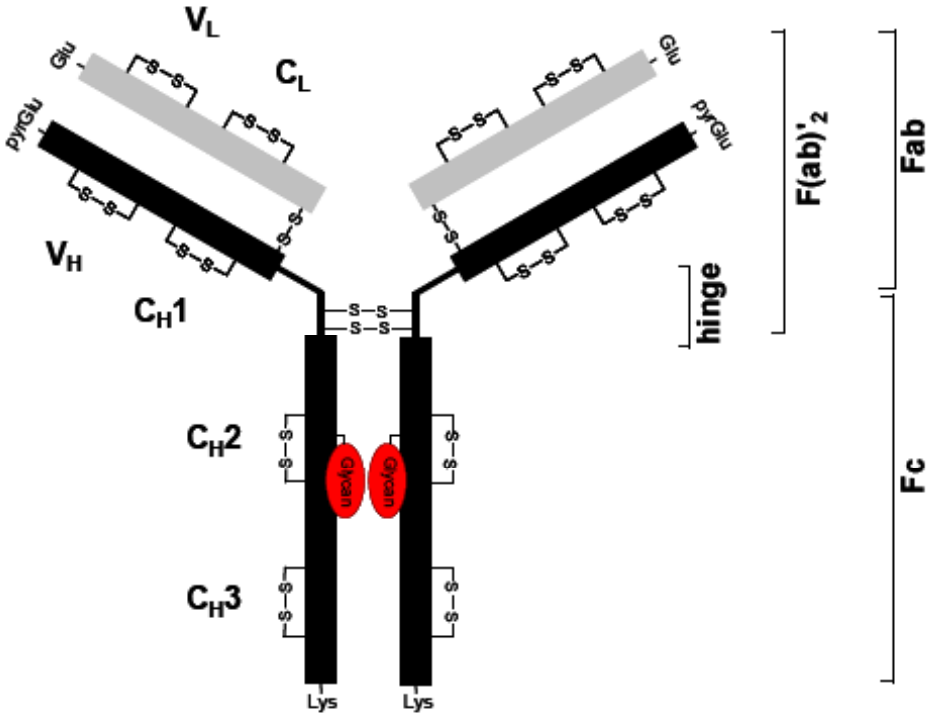


Figure 1 General structure of CNTO 148 IgG_1. The HCs (black) and LCs (gray) are shown with intra- and inter-chain disulfides, which form the Fab, hinge, and Fc regions. F(ab)'2 is a fragment comprised of two Fab regions. Amino- and carboxy-terminal residues of each chain and the general location of HC N-glycan sites in the Fc region are noted. Pyroglutamic acid (pyrGlu) is the N-terminal residue of the HC, and cysteine is the C-terminal residue of the LC.

Golimumab is a glycoprotein and exhibits multiple glycan-forms, containing two N-glycans (one on each heavy chain) with terminal galactose and sialic acid micro-heterogeneity. The glycans are bound exclusively at asparagine 306 (Asn-306) in the C_H2 region of the heavy chain and glycosylation is essentially complete at each site. The predominant sialic acid found is NGNA and the glycans contain terminal gal-α-gal linkages.

As expected golimumab displays micro-heterogeneity in terms of mass. Predicted molecular masses for golimumab range from 149,802Da to 151,064Da for the agalactosyl/agalactosyl and mono-sialyl/mono-sialyl glycol-forms, respectively. The mass calculations assume 16 disulfide bonds, two heavy-chain N-terminal pyro-glutamic acid residues, and two heavy-chain C-terminal lysine residues.

Manufacture

The golimumab drug substance (FB) is manufactured at Centocor B.V., located in Leiden, The Netherlands. The golimumab FB is shipped to Baxter Pharmaceutical Solutions, located in Bloomington, Indiana, USA, for aseptic filling into 1 mL prefilled syringes (PFS).

Golimumab formulated bulk (FB) is manufactured in a 9-stage process by continuous perfusion cell culture using SP2/0 cells followed by purification.

Cell banking processes are acceptable.

Preculture, expansion, and production are performed in Stages 1 and 2. In Stage 1, preculture is initiated from a single C524A working cell bank vial and expanded in culture flasks, disposable culture bags, and a 50 L perfusion seed bioreactor equipped with an internal spin filter. In Stage 2, the cell culture is continuously perfused in a 500 L production bioreactor using an alternating tangential flow hollow-fibre filter cell retention system (ATF system). Cell culture permeate (harvest) is collected from the ATF system. Purification of golimumab from the cell culture harvest is performed in stages 3 through 8 by a combination of affinity and ion exchange chromatography steps and steps to inactivate or remove potential virus contamination (solvent/detergent treatment and virus removal filtration). In Stage 3, harvest and/or pooled harvest is clarified and purified using affinity chromatography. In Stage 4 material is pooled for entry into Stage 5 where it is treated to inactivate any lipid-enveloped viruses potentially present. The Stage 5 reagents and impurities are removed from the golimumab in Stage 6, using cation exchange chromatography. The golimumab is further purified using anion exchange chromatography in Stage 7 to remove DNA, potentially present viruses, and impurities. In Stage 8, the purified golimumab is diluted and filtered through a virus retentive filter. Ultrafiltration of the golimumab FB is performed in Stage 9 to yield concentrated FB in the formulation excipients.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and Chemical Properties

The golimumab molecule, an IgG1κ antibody, is composed of two heterodimers. Each of the heterodimers is composed of a heavy (H) and a light (L) polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulfide linkages. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The molecular mass of the protein moiety of the antibody is around 145 kDa. In addition to the protein moiety, N-linked glycostructures are attached to Asn_{H299} of the H chain. Thus, the molecular mass of the entire glycoprotein is around 150 kDa.

Different isoforms of golimumab, as detected by isoelectric focussing (cIEF and IEF PAGE) are observed due to post-translational modifications. N-linked glycosylation constitutes the main source of heterogeneity. Neutral monosaccharide composition was indicative of a biantennal, core-fucosylated N-glycan with galactose heterogeneity. No galactosamine (from O-glycans) was detected.

Process-related impurities were shown to be removed to a consistently low level or below limit of detection.

Product-related impurities were controlled by SEC-HPLC and cSDS as part of the drug substance release criteria. Isoform profile is monitored using cIEF

Specifications

The proposed specifications for release testing of golimumab drug substance including tests for identity, potency, quantity and general attributes are acceptable and well justified. Appropriate validation data have been submitted in support of the test procedures.

Stability

The manufacturing process for golimumab formulated bulk (FB) includes two stable hold points, the pH-adjusted and filtered DPC bulk intermediate produced in Stage 3 and FB produced in Stage 9. The golimumab DPC bulk intermediate and the FB are stored frozen prior to further processing.

The requested storage temperature and proposed shelf life of golimumab DPC is 18 months at ≤ −40°C. The shelf life for golimumab DPC bulk intermediate is based on 18 months of stability data

generated at −40°C. Statistical trending analyses of the real-time stability data (−40°C) were performed when applicable as per ICH Q1E.

The requested shelf life of golimumab FB is 36 months when stored at the recommended temperature of ≤ -40°C. The shelf life for golimumab FB is based on 36 months of stability data generated at the -40°C storage condition with trending extended as per ICH Q1E.
The real time data for storage of both FB and DPC support the requested expiry periods.

Drug Product

The golimumab drug product (DP) is supplied as a sterile solution in a single-use, pre-filled syringe (PFS). It is formulated with L-histidine, sorbitol, polysorbate 80 and water for injections. The PFS comprises a 1-mL long syringe with a fixed needle, stoppered with a grey plunger stopper. The needle is covered with a needle shield. Golimumab PFS is manufactured in two dosages, a 50 mg/syringe (0.5 mL) and a 100 mg/syringe (1.0 mL). Golimumab PFS with 50 mg (0.5 mL) or 100 mg (1.0 mL) doses will be assembled into either a Centocor Autoinjector (autoinjector) or an UltraSafe Passive Delivery System (UltraSafe) for subcutaneous administration by a health care professional or a patient.

Manufacture

Manufacture of pre-filled syringe (PFS) is performed at Baxter Pharmaceutical Solutions 927 S Curry Pike Bloomington, IN 47403 USA. Assembly of the golimumab PFS with a Centocor Autoinjector or UltraSafe Passive® Delivery System, labelling, and packaging are performed at Cilag AG Hochstrasse 201 8205 Schaffhausen Switzerland.

The thawed, sterile filtered FB is filled into a 1-mL long syringe with fixed, needle, stoppered with a grey plunger stopper. The needle is covered with a needle shield. A nitrogen gas overlay is applied to the headspace in the syringe before placement of the plunger stopper.

Following 100% visual inspection, the golimumab PFS are labelled, bulk packaged and then shipped to Cilag AG (Cilag), Schaffhausen, Switzerland for assembly into either an auto-injector device or an UltraSafe. The PFS are stored at 2 to 8°C prior to labelling, device assembly, and secondary packaging. In the auto-injector assembly process, the PFS is combined with the subassemblies and device components and labelled. In the UltraSafe assembly process, the PFS is outfitted with a plunger rod, labelled, and inserted into the device.

Specifications

The specifications include control of the product in the pre-filled syringe, the pre-filled syringe in the auto-injector and the pre-filled syringe in the UltraSafe delivery system, and contain tests for identity, impurities, potency, quantity, device functionality and general attributes. Appropriate validation data have been submitted in support of the test procedures.

Stability

The company claims that the shelf life of golimumab pre-filled syringe (PFS) (50 and 100 mg/syringe) is 24 months when stored at the recommended temperature of 2 to 8°C and protected from light. The shelf life claim is based on an ongoing stability program with Phase 3 clinical and validation batches of golimumab PFS. In addition, stability data obtained with clinical batches of golimumab final vial packed product (FVP) (50 and 100 mg/vial) are used, when appropriate, to provide additional supporting evidence for the shelf life claim. The use of golimumab FVP stability data as supporting information for the shelf life claim of golimumab PFS is based on comparability studies. The stability data supports the proposed shelf-life of 24 months stored at 2°C to 8°C, protected from light.

Bioavailability

Two bioavailability studies were provided during the course of the evaluation of the submission and both studies were evaluated in full. The analytical method used to determine the levels of golimumab in subject samples was evaluated by the TGA Office of Laboratory and Scientific Services (OLSS) and found to be acceptable.

Both studies were parallel-group studies and not crossover studies. The company justified this approach based on the following factors; the long terminal half-life of golimumab (~12 days) which would lead to decreased compliance; the potential immunogenicity of golimumab and the intention of minimising subject exposure to golimumab. The quality evaluator believed that overall, the justification was reasonable.

- **Study C0524T15** investigated the overall absolute bioavailability of golimumab administered subcutaneously (SC) at three body locations - upper arm, abdomen and thigh, in healthy male subjects.

  The 100 mg golimumab 'test' injection was the same 'formulation' as that proposed for marketing but double the volume of solution proposed for marketing. The results showed an overall absolute bioavailability of ~51% after subcutaneous (SC) administration of 100 mg golimumab.

  The pharmacokinetic characteristics were similar for the subcutaneous (SC) administration of golimumab at three different body locations, namely, the upper arm, the abdomen and the thigh. However, it was brought to the attention of the Clinical Delegate that 90% confidence intervals were not determined to show strict bioequivalence and, if calculated, it is unlikely that these would fall within 80-125%.

- **Study C0524T24** investigated the bioequivalence of a single-dose subcutaneous administration of 100 mg of golimumab delivered by an autoinjector or a needle and syringe.

  Again, the study test formulation was confirmed to be identical to the 50 mg of golimumab proposed for registration, with the exception of the quantity of drug product delivered per dose (i.e. 0.5 mL for the 50 mg dose and 1.0 mL for the 100 mg dose).

  The results indicated that the two methods of subcutaneous administration of 100 mg golimumab were bioequivalent in terms of AUC_{0-t} and $AUC_{0-\infty}$, however, not for C_{max} with the C_{max} 90% confidence interval falling slightly outside the stipulated acceptance criteria of 80% to 125%, namely 127%. These results were brought to the attention of the Delegate so it could be decided if the higher C_{max} is clinically significant.

The primary statistical analyses were undertaken on the *evaluable PK population* which excluded subjects who were identified as having a "wet injection" site. "Wet injections" were defined in the study protocol as being *"A notable amount (visually estimated to be approximately 25 µL or greater) of study agent leaking out of the injection site upon removal of the autoinjector/syringe".* Eight (8) subjects (~5%) were withdrawn from the primary analysis due to wet/incomplete injections. The applicant recalculated the statistical results for the primary endpoints using data from the 8 subjects with wet injection sites who were originally excluded from the primary analyses. Bioequivalence between the two administration methods was demonstrated in terms of AUC_{0-t} and C_{max} with the 90% confidence intervals falling within the accepted 80-125% bioequivalence range (i.e. 93-117% for AUC_{0-t} and 94-124% for C_{max}). This was brought to the attention of the Clinical Delegate.

This application was presented to the 126th meeting of the Pharmaceutical Subcommittee of ADEC (PSC), which requested that the following brought to the attention of the Delegate:

- The Sponsor's justification for using parallel-designed bioequivalence studies instead of crossover designed studies was considered unacceptable as it relied on the premise that subjects would develop antibodies to golimumab and this occurs in only 5% of subjects.

- The population pharmacokinetic report only included sparse details of model development and yielded some untoward results. From this it would appear that the pharmacokinetics of subcutaneously administered golimumab are non-linear.
- Although changes in some covariates were deemed not be overly important, the population pharmacokinetic model should have been used to establish the impact of combinations of covariates. The PSC considers that this could be informative and highlight specific "worst-case" instances where dosing might be important.
- Administration with the auto injector consistently provides a greater exposure to the product than administration with the needle and syringe.

The subcommittee agreed with the quality evaluator that if there are no clinical objections to the issues mentioned above, approval of this submission can be recommended with respect to the biopharmaceutical data provided for review.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutical data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. One GMP clearance remains outstanding but otherwise all other quality matters have been resolved. As with all new biological entity, batch release testing of the first five batches by OLSS is recommended to verify quality and consistency of manufacture. Subject to the Delegate's agreement, the batch release conditions should be added to the conditions of registration of this product.

III. Non-Clinical Findings

Introduction

The nonclinical dossier was generally adequate, and influenced by ICH S6 guidelines for biotechnology-derived pharmaceuticals.

Pharmacology

Primary Pharmacology

TNF is a pro-inflammatory cytokine thought to be involved in various inflammatory and auto-immune disorders, and indications for the registered anti-TNFα mab (adalimumab, infliximab) include those proposed for golimumab. In contrast to golimumab, infliximab is a murine-human chimeric protein given by IV infusion.

As may be expected, golimumab showed a pronounced species specificity, as measured in an *in vitro* neutralisation assay of TNF cytotoxicity, which limited the available species that could be used for testing. Besides primates, golimumab showed some cross-reactivity with dog samples (crude lipopolysaccharide-stimulated monocyte supernatants were actually tested), although this species was not used. Standard rodent studies could not be carried out because mouse and rat samples were not neutralised by golimumab, but several studies used a rat/mouse chimeric mab against mouse TNFα (designated cV1q). However, these studies would be limited to demonstrating the effects of TNFα neutralisation in mice, plus any specific effects of this particular antibody preparation.

Golimumab showed its intended activity, binding *in vitro* to soluble TNFα and less potently to the transmembrane form, and neutralising TNFα cytotoxicity, for which it compared favourably with infliximab (tested concurrently). It was also active in a human TNF transgenic mouse model of arthritis with single SC doses of 1, 3, 10 and 30 mg/kg. Although demonstrating activity *in vivo*, there were no supporting toxicokinetics and the model may be of limited relevance to the clinical human disease.

Safety and Secondary Pharmacology

Separate studies were not carried out, but some investigations were conducted as part of the cynomolgus monkey toxicity studies, including blood pressure, quantitative ECG, heart and respiration rates and capillary refill times (a measure of peripheral perfusion). Urinalysis was also conducted in the long-term (25-26 weeks) IV and SC studies. Overall, no effects of treatment were identified. Additionally, humoral immunity was assessed in these studies by the measurement of anti-keyhole limpet haemocyanin (KLH) antibody responses, with only slight impairment by golimumab being seen in the one study (IV) in which an adjuvant was not used.

Complement activation by immune complexes *in vitro* was demonstrated by elicited cytotoxicity in murine cells expressing tmTNF following incubation with golimumab, suggesting a potential for similar activity *in vivo* and resulting tissue damage. There were no indications that this occurred in the toxicity studies (see *General toxicity*), although these were conducted in healthy animals rather than those showing elevated TNF. Potential interactions of golimumab with platelets or vascular endothelium were not investigated.

Pharmacokinetics and Relative Drug Exposures

Following single IV administration, golimumab clearance was prolonged in cynomolgus monkeys as in humans, but values for serum were apparently higher in cynomolgus monkeys (about 15 mL/day/kg vs 6 mL/day/kg in one study, doses of 3-5 mg/kg). Pharmacokinetic/toxicokinetic sampling periods were of extended duration and the lower values of associated terminal $t_{1/2}$ values in cynomolgus monkeys (typically 3-4 days vs 11 days in humans) were influenced by antibody responses (see below).

Inter-species comparison of golimumab exposures was not straightforward, because of the variable development of measurable or possible antibody responses and often sparse sampling schedules. However, comparison of predose concentrations suggests that drug exposures in the cynomolgus monkey studies were well in excess of that in humans treated with the recommended dose, as tabulated below. Exposures in the supporting studies in mice were also high, although these were not directly comparable as they were conducted using anti-mouse TNFα monoclonal antibody.

Table 1: Pharmacokinetic Studies with Golimumab

Species	**Duration (weeks)**	**Dose (mg/kg), route, frequency**	**$AUC_{0-\infty}$ (µg.day/mL)**	**$C_{predose}$ (µg/mL)**	**(ER)[&]**
General toxicity					
Mouse	26	10, 40 IV weekly*		255, 654 (d 182)[#]	>250
Cyno. monkey	4	10, 50 IV weekly		35, 694 (day 28)	>30
Cyno monkey	25	25, 50 IV weekly	5809, 11634 (d 168)	515, 1288 (d 176)	>500
Cyno. monkey	26	25, 50 SC 2x/week	2621, 5657 (d 179)	988, 2012 (d 179)	>900
Reproductive toxicity(all females)					
Mouse	4	10, 40 IV weekly		85, 571 (GD 11)[$]	na
Mouse	GD 6-12	10, 40 IV twice		37.5, 159 (GD 14)[§]	na
Mouse	GD 6-PPD 15	10, 40 IV 6 times		43, 240 (PPD 15)[x]	na
Mouse	GD 6-PPD 15	40 IV 6 times		609 (PPD 15)[x]	na
Cyno. monkey	GD 20-51	25, 50 SC 2x/week	10025, 27052 (GD 51)[†]	553, 1362 (GD 51)	>550
Cyno. monkey	GD 50-PPD 33	25, 50 SC 2x/week		666, 1811 (GD 145)	>660

* cV1q anti-mouse TNFα tested, [#] 8 days after the last dose, [&] $C_{predose}$ relative to a human value of about 1 µg/mL (section 7.2.3), [$] 4 days after the last dose, [†] GD 51-86 [§] 2 days after the last and second dose, [x] 4 h after last dose

GD and PPD = gestation and post-partum days, na = not applicable

Additionally, an $AUC_{0\text{-}2\ week}$ value of 132 µg.day/mL was quoted in the nonclinical summary for clinical study C0524T01 (50 mg SC every 2 weeks x 10 weeks, uveitis patients), although this was not included in the clinical overview or summary. Golimumab exposures in the SC and IV cynomolgus monkey toxicity studies were clearly well in excess of that in humans after adjustment for dosing every 4 weeks (x0.5 = 66 µg.day/mL).

Golimumab was immunogenic in cynomolgus monkeys, with generated antibody potentially interfering with the drug assays and influencing measured clearance and $t_{1/2}$ values, as well as possibly resulting in enhanced clearance via the formation of antigen-antibody complexes. Immunogenicity in cynomolgus monkeys has also been shown for other anti-TNFα mab, such as adalimumab, together with antibody interference with ELISA drug measurements. However, the high doses and frequent administration used in the long-term IV and SC toxicity studies in cynomolgus monkeys achieved high systemic drug exposures (see Table 1), despite the probable occurrence of immune responses. Although this was seen only in 1/32 animals in both studies, the true incidence and extent of antibody responses could not be determined with the method used because of assay interference by high drug concentrations. Elimination $t_{1/2}$ values were also higher (11-18 days) than following single administration of lower doses. The immunogenicity of golimumab did not result in any untoward effects in cynomolgus monkeys, as there were little or no effects of treatment in the toxicity studies (see *General Toxicity*). Antibody responses were also observed in the clinical trials, affecting about 4% of subjects and with about half of responses involving neutralising antibody.

Standard pharmacokinetic studies of metabolism and excretion were not conducted, which is acceptable for an agent such as golimumab, although it would have been useful to have determined tissue distribution to show that it gained access to sites of action (e.g. synovial fluid). Such

distributions were apparently not investigated in the clinical trials. However, golimumab was shown to readily cross the placenta to the fetus in cynomolgus monkeys, as was cV1q mab in mice.

Toxicology

Golimumab was well tolerated in the long-term IV and SC toxicity studies in cynomolgus monkeys, with the only identified effects of treatment being slight and variable increases in peripheral blood T- and B-cells. One low dose animal treated IV (1/16) showed evidence of disseminated fungal infection, possibly resulting from an impaired host defence resulting from golimumab treatment, although humoral immunity was largely unaffected (see *Safety and secondary pharmacology*). Increased susceptibility to infections is a well-known effect of anti-TNF therapy (Pfeffer, 2003), which may be expected to be exacerbated by the concurrent use of immunosuppressants such as methotrexate. The proposed Product Information contains a warning about the risk of infections. Minor injection site histological inflammation seen in the SC study may be related to generated anti-golimumab antibody responses (see *Pharmacokinetics and relative drug exposures*). It should be noted that golimumab was not tested in combination with methotrexate, which is a proposed treatment combination.

The lack of golimumab toxicity in adequate studies is consistent with a high specificity and a demonstrated lack of cross-reactivity with tissue components. In an *in vitro* screening study using an adequate range of human tissues (cryostat sections), slight binding of biotin-labelled drug was seen only to skin and mammary gland nipple epidermal epithelium. This most likely reflected the presence of the TNFα and its p55 receptor reported to be present in normal human skin epidermis (Kristensen *et al*., 1993). Product from 2 different cell lines was used in early and later studies, with the latter also being the source of the commercial preparation. Suitable bridging studies demonstrated comparability of the different cell line products. The pivotal cynomolgus monkey toxicity studies (including reproductive) used the C524D cell-derived product.

A supporting 26 week toxicity study was conducted in mice, again with no identified effects of treatment (apparently transient ophthalmic findings appeared to be incidental), but this was not directly comparable because of the use of an anti-mouse TNFα mab (cV1q). This mab bound to soluble TNF and inhibited its cytotoxicity, and elicited complement-dependent lysis of cells expressing tmTNF *in vitro*. It is of interest, therefore, that it did not elicit any untoward effects in mice, although healthy animals were used rather than those with elevated TNF. According to the nonclinical summary, this and other mouse studies were conducted in support of the application for infliximab by the same sponsor.

Testing of golimumab in rodents was not appropriate because of lack of pharmacological activity against human TNF, as noted above (*Primary pharmacology*). Some cross-reactivity was seen with dog TNFα, and this could possibly have been used as a second species for testing golimumab, although the IC_{50} for neutralisation in the *in vitro* assay in which this was tested was relatively high (242 nM or about 36 µg/mL). Based on predose concentrations in the cynomolgus monkey studies (Table 1), such a serum concentration would be achievable in dogs, but the usefulness of a study in dogs is questionable given the lack of effect in primates. The ICH S6 guideline suggests that normally 2 relevant species should be used for the testing of biotechnology-derived pharmaceuticals but that one may suffice, and the use of only one species is acceptable for the current application. Only one species (cynomolgus monkey) was used for long-term toxicity testing of adalimumab, despite a relatively high degree of cross-reactivity with dog TNFα.

Genotoxicity and Carcinogenicity

No studies were conducted, which is acceptable as these are not appropriate for an agent such as golimumab. Anti-TNFα therapy in general is known to be immunosuppressive and as such is

possibly associated with an increased incidence of lymphomas. The proposed Product Information includes a section on malignancies.

Reproductive Toxicity

Despite a demonstrated high degree of golimumab placental transfer (high-dose fetal/maternal serum ratio of 0.9), there were no adverse effects in the embryofetal development study conducted in cynomolgus monkeys. Dosing was during the period of organogenesis (gestation days 20-51), but fetuses were likely to have been exposed for a longer duration based on a maternal serum half-life of 10-11 days. Although the intended clinical dosing frequency is much lower (once monthly vs twice weekly in cynomolgus monkeys), there is the possibility of significant serum levels in newborns of treated mothers, which may be associated with immunosuppression and increased susceptibility to infections.

Such effects were not observed in a pre-/post-natal study in this species, although assessments of immunotoxicity (peripheral blood lymphocyte phenotyping, humoral and cell-mediated responses) were conducted well after the last maternal dose on post-partum day 33. Additionally, this provides some evidence for a lack of effect of maternal treatment (initiated on gestation day 50) on the development of the offspring immune system as well as any acute immunosuppressive effect. Overall, there were no adverse effects of maternal dosing on offspring development in this study despite demonstrated high neonatal serum drug concentrations (e.g. 219-536 µg/mL on post-partum day 15). It is difficult to reconcile such high values, however, with the relatively low concentrations in milk (about 0.8-3.7 µg/mL on post-partum days 14-28) and these probably include a transplacental contribution. It is also noteworthy that the golimumab serum half-life was high in neonates (about 23 days) as in dams, for which values of about 10-30 days (both studies) compared with 14-16 days obtained in the 26 week general toxicity study using the same dosing protocol.

Supporting studies in mice (IV dosing) showed that the anti-mouse TNFα mab used also readily crossed the placenta and was present in milk at low concentrations (0.9-3.1% of maternal serum values). Findings, which included deaths (possibly related to hypersensitivity) and slightly lower pregnancy rates in a fertility and early embryonic development study, and reduced offspring viability in a pre-/post-natal study (also seen with a control antibody), appeared to be incidental or of uncertain relevance to golimumab. It is noteworthy that there were no effects of treatment in an embryofetal development study, although only 2 doses were given (on gestation days 6 and 12) and as noted above, these studies would be expected to reveal effects of TNFα inhibition and any specific activities of this particular preparation. Although a small reduction in fertility was observed at 40 mg/kg/week in a study in which both sexes were treated, this was not apparent at 10 mg/kg/week, a dose resulting in a high serum concentration (85 µg/mL at 4 days post-dosing).

Local Tolerance

Golimumab single- and multiple-dose SC local tolerance studies, carried out in cynomolgus monkeys, did not replicate the intended clinical use. The solution concentration was the same (100 mg/mL), but the formulation was different and injection volumes were lower (about 0.25 mL vs 0.5 mL) in 2 studies, or higher (1.13 mL) in one study that excluded histological examination. Only minor local reactions were observed, but it was noteworthy that mild chronic vasculitis was seen in 1/4 animals that showed the highest antibody titre in a 4 week study with 2x weekly injections. A similar change was noted in 1/4 human immunoglobulin controls although the immune status of this animals was unknown. As noted above (*General toxicity*), minor last injection site inflammation was seen in the 26 week SC cynomolgus monkey study (which did not use the proposed formulation), and this may have been related to anti-golimumab antibody responses.

A low incidence of mild-moderate injection site reactions (mainly erythema) was apparently observed in the phase 3 clinical trials (Clinical Overview).

Non-Clinical Summary and Conclusions

Summary

- Golimumab bound to soluble and transmembrane (tm) TNFα *in vitro* with a slightly higher potency than infliximab, and it showed a strong species specificity in cytotoxicity neutralisation assays using lipopolysaccharide-stimulated monocyte medium as a source of TNFα. Cross-reactivity ranged from moderate (cynomolgus monkey; IC_{50} = 40 ng/mL vs a human value of 4 ng/mL) to absent (mouse and rat). Activity was demonstrated in a human TNF transgenic mouse arthritis model (1 to 30 mg/kg single SC dose).

- Only minor binding of golimumab to skin epidermal epithelium was observed in cross-reactivity studies with a panel of human tissues using immunohistochemical staining. Separate safety pharmacological studies were not conducted, but some investigations were incorporated into the cynomolgus monkey toxicity studies, with no treatment-related findings. Humoral immunity (keyhole limpet haemocyanin antigen) was slightly reduced after IV but not SC administration.

- Golimumab was immunogenic in cynomolgus monkeys and antibody development interfered with enzyme immunoassay measurements (the reverse was also true). Clearance was about 15 mL/day/kg after single IV administration in this species, and measured terminal $t_{1/2}$ values were typically 3-4 days. SC bioavailability was high (>75%). Standard distribution, metabolism and excretion studies were not conducted, which is acceptable.

- Repeat-dose toxicity studies were carried out in cynomolgus monkeys with weekly IV (4 and 25 weeks) or twice weekly SC (26 weeks) administration and high-doses of 50 mg/kg, with few effects of treatment. Systemic drug exposures based on predose concentrations were much higher than the human values with the recommended dose (>500 fold). Flow cytometry analysis of peripheral blood lymphocyte showed tendencies for slight variable increases in T-cell subsets and B-cells. A supporting 25 week weekly IV study in mice was also conducted using a mab directed against murine TNFα (cV1q), with no toxicity being seen. cV1q would be expected to show the effects of TNFα neutralisation in mice and any specific activity of this particular mab.

- There were no genotoxicity and carcinogenicity studies, which is acceptable. Reproductive toxicity studies were conducted with golimumab in cynomolgus monkeys (embryofetal development, pre- and post-natal; high-dose of 50 mg/kg SC twice weekly). Supporting studies were carried out with cV1q in mice (fertility and early embryonic development, embryofetal development, pre-/postnatal), although these were probably of limited relevance to golimumab use. Slightly reduced fertility was observed with cV1q at 40 mg/kg/week but not at 10 mg/kg/week.

- Golimumab readily crossed the placenta to the fetus in cynomolgus monkeys, but only low concentrations were measurable in milk (<1% of maternal serum values). No effects of treatment were seen in either of the cynomolgus monkey studies, although serum concentrations were high in dams (approx. 300-1500 µg/mL with the high-dose over the dosing period) and neonates (219-537 µg/mL at 15 days of age).

Conclusions

Intended pharmacological activity of golimumab was demonstrated *in vitro*, and use of a human TNF transgenic mouse model showed that it was active *in vivo*. Adequate toxicity studies were

primarily conducted in cynomolgus monkeys because of a strong species specificity, which would be expected, with no findings that would preclude approval for registration. There were, however, no studies using golimumab in combination with methotrexate.

Adequate reproductive studies in this species showed no untoward effects of golimumab treatment, although these did not include investigation of fertility, which would not be practical. Slightly reduced fertility was observed in a mouse study using a high dose of an analogous antibody specific for mouse TNFα, but the relevance of this to golimumab use in humans is uncertain.

Recommendation

There were no non-clinical findings that precluded approval of the submission. Repeat dose toxicity studies in monkeys using high doses of golimumab showed few treatment effects (slight increases in T-cell subsets and B-cells) and an intravenous study in mice showed no toxicity. Golimumab was generally well tolerated in the toxicity studies, which is consistent with its high specificity and lack of cross-reactivity with tissue components. Minor binding to skin epithelium was seen. Golimumab was immunogenic in monkeys but this did not result in untoward effects. No genotoxicity or carcinogenicity studies were conducted, as expected for this type of product. Reproductive toxicity studies showed slightly reduced fertility at high doses in mice (40mg/kg/week) but not at lower doses. Golimumab crosses the placenta and was measured in low concentrations in maternal milk. Minor injection site reactions were seen, including mild vasculitis with 2x weekly injections. No studies were done in combination with methotrexate.

IV. Clinical Findings

Introduction

Golimumab is a new biological entity. It is a fully human IgG1k anti-TNF alpha monoclonal antibody produced from a recombinant murine cell line. The submission represented a complete development program for the new biological entity. There were 14 clinical studies, of which 5 were pivotal (3 in rheumatoid arthritis, 1 in psoriatic arthritis and 1 in ankylosing spondylitis) and their extensions that cover 3195 subjects, 2357 of whom received golimumab. There were also additional studies performed on pooled data and *in vitro* studies performed on samples collected during the clinical studies.

There were four studies conducted primarily to examine pharmacodynamics, two of which were clinical studies conducted in 88 subjects, 69 of whom were treated with golimumab:

Study C0466T01 36 subjects, 26 received golimumab

Study C0466T02 52 subjects, 43 received golimumab

Study CP2006T-049 and ***Study CP2007T-042*** were *in vitro* studies analysing samples from Study C0524T02.

There was one bioequivalence study conducted in 156 subjects, all of whom received golimumab:

Study C0524T24 156 subjects, all received a single dose of golimumab

There were three studies conducted in 390 subjects, 312 of whom received golimumab, evaluable primarily for pharmacokinetics:

Study C0524T13 30 subjects, all received a single dose of golimumab

Study C0524T23 51 subjects, all received golimumab

Study C0524T03 309 subjects, 231 received golimumab

In addition there were three population pharmacokinetic analyses that used data collected during the efficacy studies: ***Study POP-PK-AS***, ***Study POP-PK-PSA*** and ***Study POP-PK-RA***.

There were six studies conducted in 2475 subjects, 1801 of whom received golimumab, evaluable for efficacy:

Study C0524T09-24wk GO-RAISE, 356 subjects, 278 received golimumab

Study C0524T08-24wk GO-REVEAL, 405 subjects, 292 received golimumab

Study C0524T02, 172 subjects, 137 treated with golimumab

Study C0524T05-24wk GO-BEFORE, 637 subjects, 477 treated with golimumab

Study C0524T-06-24wk, 444 subjects, 311 treated with golimumab

Study C0524T11-24wk GO-AFTER, 461 subjects, 306 treated with golimumab

There was one additional study conducted using golimumab evaluable only for safety:

Study C0524T01, 26 subjects, 19 received golimumab

In addition there was one study for safety conducted using the autoinjector device:

Study C0999D01, 60 subjects, none received golimumab.

All the studies appear to have been conducted according to Good Clinical Practice, and in accordance with the principles of the Declaration of Helsinki.

Pharmacokinetics

Bioequivalence Studies

Study C0524T24 was a phase 1, randomised, open-label, parallel-design, inpatient/ outpatient study to assess the bioequivalence of a single-dose subcutaneous administration of golimumab delivered by the Centocor autoinjector or a needle and syringe in healthy subjects. Prior to the bioequivalence study there was a training component where 47 subjects at each of two study centres received a single subcutaneous injection of 1.0 mL placebo by one of the two injection methods. Golimumab concentrations were measured on Days 1 through 8 and on Days 15, 22, 29, 36, 43, 50, and 71. Golimumab was delivered as a single 100 mg (supplied as 1.0 mL sterile liquid) subcutaneous injection delivered by one of two drug injection methods: the Centocor autoinjector or a needle and syringe. The injection site was the abdominal wall for all study subjects. The study included healthy adult males aged 18 to 50 years, with BMI 23 to 30 kg/m^2, inclusive, and weight 60 to 90 kg who had no history or evidence of latent or active TB and no exposure to TB or other infectious diseases.

A total of 156 subjects were entered into the study: 79 in the needle and syringe group and 77 in the autoinjector group. The two injection methods were bioequivalent for $AUC_{(0\text{-}49D)}$. The 90% CI for the ratio of geometric mean $AUC_{(0\text{-}49D)}$ values between the two injection methods was 95.17% to 120.55%, which fell between the prespecified 80% and 125% range. However, the 90% CI for Cmax was 96.14% to 127.42%, which fell slightly outside the 80% to 125% range. The 90% CIs for AUC_{last} and AUC_{inf} were 95.84% to 122.21%, and 93.91% to 119.38%, respectively.

Evaluator's comments: The bioequivalence study demonstrated that administration of golimumab using the autoinjector device was bioequivalent to injection by needle and syringe.

Pharmacokinetic Studies

Study C0524T13 was an open-label, single-dose, single period, in-patient/out-patient study of golimumab pharmacokinetics in healthy adult male subjects. The study included 30 healthy male volunteers aged 18 to 45 years, BMI of 23-30 kg/m^2, and weight of 60-90 kg, with no clinically

relevant abnormalities. Subjects were excluded if they had a history of latent or active granulomatous infection, including TB, recent opportunistic infection, or recent close contact with a person with active TB. Each subject received: golimumab 100mg in 1 mL injected subcutaneously to the abdomen. Serum golimumab concentrations were determined at 1 hour prior to dosing, 12 hours after dosing, and at Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 22, 29, 36, 43, 50, 57, 64, and 71. Serum golimumab concentrations were measured using a validated electrochemiluminescent immunoassay (ECLIA) method. A validated enzyme-linked immunosorbent assay (ELISA) was used to determine antibodies to golimumab in serum samples taken 1 hour prior to dosing and 70 days following dosing.

Serum golimumab concentrations were measurable through to 49 days post dosing for most subjects. Tmax was at a median time of 3.5 days. Golimumab median terminal half-life of 11.0 days and apparent clearance was 1.35 L/day. There was a moderate degree of inter-subject variability for Cmax, AUC(0-49D) and AUCinf with coefficients of variation (CV%) of 35.72%, 32.02% and 36.24% respectively.

Study C0524T23 was a single-blind, partially-randomised study consisting of 2 groups (Japanese and Caucasians) and each group consisted of 2 dose arms: 50 mg and 100 mg. Japanese subjects were sequentially randomised to receive either a 50 or 100 mg SC administration of golimumab. Serum golimumab concentrations were measured predose, at 12 hours after dosing on Day 1, and on Days 2, 3, 4, 5, 6, 7, 8, 11, 15, 22, 29, 36, 43, and 50. Antibodies to golimumab were assessed prior to treatment and on Day 50. Follow-up was to Day 79. The study treatments were: golimumab 50 mg (0.5 mL) or 100 mg (1.0 mL) as a single subcutaneous dose. The study included 51 healthy male volunteers, aged 20 to 45 years, with body mass index of 19 to 30 kg/m^2, and weight of 50 to 90 kg. Caucasian subjects were matched by body weight (±20%) to a Japanese subject and both were administered a corresponding dose (50 or 100 mg SC injection) of golimumab. There were 12 subjects in each of the Japanese dosing groups, 14 in the 50 mg Caucasian group and 13 in the 100 mg Caucasian group. The pharmacokinetic parameters were similar for Japanese and Caucasian subjects. The exposure to golimumab increased with dose, but was not dose proportional in that a greater exposure, for the magnitude of the dose, occurred with the 100 mg dose.

Study C0524T03 was a multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study in subjects with severe persistent asthma. The study included males or females ≥18 years of age, with severe persistent asthma who were symptomatic despite treatment with high dose ICS and long-acting β2 agonist (LABA), with or without continuous oral corticosteroid. The study treatments were:

1. 75 mg at Week 0 then 50 mg every 4 weeks to 52 weeks

2. 150 mg at Week 0 then 100 mg every 4 weeks through to 52 weeks

3. 300 mg at Week 0, then 200 mg every 4 weeks to 52 weeks

4. placebo

The coprimary endpoints were change from baseline to Week 24 in prebronchodilator clinic-measured, percent-predicted, forced expiratory volume in one second and number of severe exacerbations from baseline through Week 24. The safety outcome measures were: adverse events (AEs), serious adverse events (SAEs), laboratory values, vital signs, the incidence of antibodies to golimumab, and development of antinuclear antibodies (ANA) or anti-double-stranded DNA (anti-dsDNA) antibodies by treatment group.

A total of 309 subjects were enrolled and randomised to treatment: 78 to placebo, 77 to golimumab 50 mg, 76 to golimumab 100 mg and 78 to golimumab 200 mg. Of the randomised subjects, 173

(56.0%) were female, 136 (44.0%) were male and the age range was 19 to 81 years. There were no differences between the treatment groups in efficacy outcome measures.

The pharmacokinetics of golimumab were linear. The AUC(0-28 day) increased proportionally with dose: median AUC(0-28 day) of 60.88 µg•day/mL, 112.54 µg•day/mL, and 264.45 µg•day/mL for the 50 mg, 100 mg, and 200 mg dose groups, respectively. Median Cmax increased proportionally with dose: 4.42 µg/mL, 8.90 µg/mL, and 15.50 µg/mL for the 50 mg, 100 mg, and 200 mg dose groups, respectively. The median t_{max} for all doses was approximately 4 days. The median half-life of golimumab ranged from 9.39 days to 12.58 days. Median volume of distribution was similar across all groups: 19.28 L, 19.51 L, and 17.00 L for the 50 mg, 100 mg, and 200 mg dose groups. Median clearance did not change with dose: 1.03 L/day, 1.01 L/day, and 1.07 L/day for the 50 mg, 100 mg, and 200 mg dose groups, respectively.

Pharmacokinetic data from studies described under Pharmacodynamics

In ***Study C0466T01***, C_{max} was dose proportional. T_{max} remained constant. $AUC_{(0-14)}$ was dose proportional, AUC increased slightly with increasing dose. T½ increased with increasing dose. Clearance remained constant. Volume of distribution (Vz) increased with increasing dose.

In ***Study C0466T02***, the single dose pharmacokinetics of golimumab appeared to be linear except for the 1.0 mg/kg dose group where C_{max} was lower than expected and clearance higher. The steady state pharmacokinetics of golimumab appeared to be dose dependent over the range 0.3 mg/kg/dose to 1.0 mg/kg/dose.

Study POP-PK-AS was a population pharmacokinetic study using data from Study C0524T09 conducted using subjects with ankylosing spondylitis (AS). The population pharmacokinetic analysis was performed using NONMEM version 6. The covariates were: age (years), body weight (kg), height (cm), body surface area (BSA, m^2), renal function using estimated creatinine clearance (CRCL, mL/min), hepatic function (AST [U/L], ALT [U/L], and albumin [g/dL]), disease duration from initial diagnosis (years), baseline disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], CRP [mg/dL]), and white blood cell (WBC) count ($\times 10^9$/L). The study doses were: golimumab 50 mg and golimumab 100 mg.[1] There were six doses at 4 weekly intervals administered subcutaneously. Subjects in the placebo group were switched to active treatment with golimumab 50 mg if there was <20% improvement from baseline at Weeks 16 and 20. Subjects in the golimumab 50 mg group were switched to active treatment with golimumab 100 mg if there was <20% improvement from baseline at Weeks 16 and 20. Data from all subjects who received at least one active administration of golimumab and who also had at least one measurable serum concentration were included in the data set. There were 1,983 concentrations from 312 subjects, mean (SD) of 6.4 (2.3) concentrations per subject. The age range was 18 to 83 years, weight 35 to 142 kg, height 148 to 196 cm, BSA 1.3 to 2.6 m^2, disease duration 0.2 to 39.8 years, BASDAI 1.8 to 10, CRP 0.3 to 10.3 mg/dL, WCC 2.6 to 14.4 $x10^9$/L, albumin 3.2 to 5.2 g/L, ALT 6.0 to 133.0 U/L, AST 8.0 to 99.0 U/L, CRCL 47.6 to 215.9 mL/min. There were 225 (72.1%) males in the study.

The base model was a one-compartment PK model with first-order absorption and elimination. The final covariate model was described and the covariates that influenced the pharmacokinetic parameters were: body weight, CRP, sex and presence of golimumab antibodies (IRP). There were ten subjects who tested positive for antibodies and these subjects appeared to have 36% higher CL/F. Concomitant use of methotrexate, sulfasalazine or oral corticosteroids did not significantly

[1] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): Subject self-assessment using a VAS (0 to 10 cm) on the following criteria – (A) fatigue, (B) spinal pain, (C) joint pain, (D) enthesitis, (E) qualitative morning stiffness, (F) quantitative morning stiffness. The BASDAI = 0.2 (A + B + C + D + 0.5[E + F]).

influence the population PK parameters. Neither hepatic nor renal function significantly influenced the population PK parameters.

Study POP-PK-PSA was a population pharmacokinetic study using data from Study C0524T08 conducted in patients with psoriatic arthritis. The population pharmacokinetic analysis was performed using NONMEM V6. The covariates were: age (years), body weight (kg), height (cm), BSA (m^2), renal function using estimated creatinine clearance (CRCL, mL/min), hepatic function: AST (U/L), ALT (U/L), and albumin (g/dL), disease duration from initial diagnosis (years), baseline disease activity (Psoriasis Area Severity Index [PASI] score, Disease Activity Score including a 28-joint count using CRP [DAS28C], tender joint count (TJC), swollen joint count (SJC), and CRP [mg/dL]), and white blood cell (WBC) count ($\times 10^9$/L), sex, and concomitant medications (DMARD, NSAID and corticosteroids).[2,3] The study treatment was golimumab 50 mg or 100 mg by subcutaneous injection at 4 weekly intervals for up to six doses. At Week 16 (Dose 5) patients randomised to placebo who had <10% improvement from baseline in both swollen and tender joints were transferred to the 50 mg group, and those in the 50 mg group who had <10% improvement from baseline in both Swollen Joint Count (SJC) and Tender Joint Count (TJC) were transferred to the 100 mg group. Data from all subjects who received at least one administration of golimumab and at least one measurable serum concentration were included in the data set.

There were 2,029 measurable serum concentrations of golimumab from 337 subjects. The mean (SD) number of observations per subject was 6.0 (2.5). The age range was 20 to 78 years, weight 43 to 191 kg, height 145 to 194 cm, BSA 1.3 to 2.9 m^2, disease duration 0.3 to 44.5 years, PASI score 0 to 51, DAS28C 2.0 to 6.9, SJC 3 to 56, TJC 3 to 68, CRP 0.3 to 12.1 mg/dL, WCC 2.6 to 15.6 x10^9/L, albumin 3.5 to 5.1 g/dL, ALT 7 to 98 U/L, AST 9 to 61 U/L, CrCL 50.6 to 258.8 mL/min. There were 202 (59.9%) subjects that were male.

The base model was a one-compartment PK model with first-order absorption and elimination, a between subject variability (BSV) on CL/F and V/F, a correlation between BSV on CL/F and BSV on V/F, and residual variability described by a proportional model. The final covariate model was

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[2] Psoriatic Area and Severity Index: The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of disease is calculated as follows. In the PASI system, the body is divided in to four regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of total body surface area (BSA), respectively. Each of these areas is assessed separately for erythema, induration, and scaling, which are each rated on a scale of 0 to 4. The scoring system of the signs of the disease (erythema, induration, and scaling) are 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement of psoriatic lesions is – (0) = no involvement, (1) = 1% to 9% involvement, (2) = 10% to 29% involvement, (3) = 30% to 49% involvement, (4) = 50% to 69% involvement, (5) = 70% to 89% involvement, (6) = 90% to 100% involvement. To help with area assessments, the following conventions should be noted - the neck is considered part of the head, the axillae and groin are part of the trunk, and the buttocks are part of the lower extremities

The PASI formula is PASI = 0.1 (Eh + Ih + Sh) Ah + 0.3 (Et + It + St) At + 0.2 (Eu + Iu + Su) Au + 0.4 (El + Il + Sl) Al where E = erythema, I = induration, S = scaling, and A = area.

[3] Disease Activity Index Score 28: The Disease Activity Index Score 28 (DAS28) is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and Global Health (GH). The DAS28 is a continuous parameter and is defined as follows: DAS28 = 0.56* SQRT(TEN28) + 0.28*SQRT(SW28) + 0.36* Ln (CRP+1) + 0.014*GH + 0.96. TEN28 is 28 joint count for tenderness. SW28 is 28 joint count for swelling. The set of 28 joint count is based on left and right shoulder, elbow, wrist, metacarpophalangeal (MCP)1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP)1, PIP2, PIP3, PIP4, PIP5 joints of upper extremities and left and right knee joints of lower extremities. Ln (CRP+1) is natural logarithm of (CRP value + 1). GH is Patient's Global Assessment of Disease Activity on VAS of 100 mm.

described. Clearance increased with body weight, CRP, antibodies to golimumab (IRP) and smoking. Antibodies to golimumab increased clearance by 10% and smoking increased clearance by 13%. Volume of distribution was influenced by body weight. Concomitant treatment with DMARDs, NSAIDs, or corticosteroids did not influence golimumab pharmacokinetics. Hepatic or renal disease did not influence golimumab pharmacokinetics.

Study POP-PK-RA was a population pharmacokinetic study using data from Studies C0524T05 and C0524T06 conducted using patients with rheumatoid arthritis (RA). The population pharmacokinetic analysis was conducted using NONMEM Version 6. The covariates were age, body weight, height, body surface area, estimated creatinine clearance, hepatic function (AST, ALT, albumin), disease duration from initial diagnosis, baseline disease activity (Disease Activity Score including a 28-joint count using CRP [DAS28C], TJC, SJC, and CRP), white blood cell count, sex and concomitant treatment (methotrexate [MTX], NSAIDs, corticosteroids). The study treatments were golimumab 50 mg or 100 mg at 4 week intervals for up to 48 weeks. Data from all subjects who received at least one administration of golimumab and who also had at least one measurable serum concentration were included in the data set.

The analysis included 3,411 measurable concentrations from 594 subjects. The mean (SD) number of observations per subjects was 5.7 (2.2). The age range was 18 to 85 years, weight 37.5 to 167.8 kg, height 139 to 200 cm, BSA 1.3 to 2.6 m^2, disease duration 0.1 to 49.6 years, DAS28C 2.5 to 7.7, SJC 3 to 55, TJC 4 to 68, CRP 0.3 to 19.9 mg/dL, WCC 2.7 to 23.3 $x10^9$/L, albumin 3.0 to 5.7 g/dL, ALT 4 to 216 U/L, AST 8 to 125 U/L, CrCL 32.2 to 278.4 mL/min, 111 (18.6%) subjects were male, and 392 (65.9%) subjects received concomitant MTX.

The base model was a one-compartment PK model with first-order absorption and elimination, with a between-subject variability (BSV) on CL/F, V/F, and first-order absorption rate constant (Ka), a correlation between BSV on CL/F and BSV on V/F, and residual variability described by a proportional model. The final covariate model was described. Clearance was increased by increasing body weight, CRP and presence of golimumab antibodies (IRP) and decreased by concomitant MTX treatment. Presence of golimumab antibodies increased clearance by 29%. Concomitant MTX decreased clearance by 17%.

Evaluator's comments: Although the pharmacokinetics of golimumab are for the most part linear, there was greater exposure (as measured by AUC) with increasing dose. The pharmacokinetic parameters of golimumab were similar for Japanese and Caucasian subjects. The pharmacokinetic parameters in subjects with severe asthma were similar to healthy volunteers. The pharmacokinetic parameters were not influenced by hepatic or renal disease. Clearance and volume of distribution were primarily determined by body weight. Clearance decreased with increasing CRP. Clearance of golimumab was increased in the presence of anti-golimumab antibodies by 10% to 36%. Clearance of golimumab was increased in smokers by 13%. Concomitant use of methotrexate, sulfasalazine or oral corticosteroids did not significantly influence the population PK parameters. Clearance of golimumab was decreased by concomitant MTX treatment by 17%.

Drug Interactions

There were no drug interaction studies presented.

Pharmacodynamics

Study C0466T01 was a randomised, double-blind, placebo-controlled study in which adult subjects with active rheumatoid arthritis (RA) received a single IV infusion of golimumab or placebo. Subjects were assessed for pharmacokinetics, pharmacodynamics, efficacy, safety, immune function, and antibody response to golimumab for 16 weeks. The treatment doses were: golimumab 0.1, 0.3, 1, 3, 6, or 10 mg/kg as a single intravenous dose, infused over a period of 2 hours, compared with intravenous placebo. A total of 36 subjects were entered into the study and all completed. Three subjects were randomised to 0.1 mg/kg, three to receive 0.3 mg/kg, five to

receive 1 mg/kg, five to receive 3 mg/kg, five to receive 6 mg/kg, five to receive 10 mg/kg and ten to receive placebo.

The inclusion criteria included: male or female ≥18 years of age with active RA for ≥3 months from onset of persistent synovitis. Subjects were allowed to be on a stable therapeutic regimen of up to two DMARDs, oral corticosteroids, and/or NSAIDs, for the treatment of their arthritis. Intramuscular, intra-articular, and IV steroids were not allowed within 4 weeks of study agent administration and for the duration of the study.

The outcome measures included:

- Pharmacokinetic parameters
- Pharmacodynamic parameters: TNF-α, interleukin 6 (IL-6), interleukin 1 beta (IL-1β), interleukin 8 (IL-8), monocyte chemotactic protein (MCP-1), vascular endothelial growth factor (VEGF), transforming growth factor β1 (TGF-β1), soluble intercellular adhesion molecule 1 (sICAM-1), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 3 (MMP-3), receptor activator of NFκB (RANK) ligand, and annexin V staining
- Efficacy outcome measures: Individual C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values over time; improvement from baseline in the signs and symptoms of RA was evaluated using the proportion of subjects achieving an ACR 20 response through week 16; fatigue and morning stiffness.[4]

For the pharmacodynamic end-points no hypothesis tests were performed, and little difference was apparent between the treatment groups. TNF-α, IL-6, IL-8, MCP-1, TGFβ1, MMP-1, MMP-3, and RANK ligand levels did not alter with dose, compared with placebo or over time. The results for VEGF, ICAM-1, and MMP-3 in subjects receiving golimumab were interpreted by the Sponsor as indicating a trend towards decrease compared to placebo, and this was best illustrated by VEGF. VEGF levels were interpreted as dropping by Week 4, then rising again by Week 8. Annexin V and AAD staining did not appear to change over the 24 hours post dosing.

For the efficacy endpoints:

- ACR 20 showed little difference between golimumab and placebo.
- CRP improved from Day 7 through to Week 4, with plateau of effect from 3 mg/kg.
- ESR improved through to Week 4, with plateau of effect at the 6 mg/kg dose.

Study C0466T02 was a double-blind, placebo-controlled two-stage study in patients with RA. In Stage I, subjects were randomised to receive a single dose of either golimumab or placebo. The decision to proceed with Stage II was based on the safety assessment of Stage I. In Stage II, subjects were randomised to receive three subcutaneous doses of placebo or golimumab at two week intervals and followed up for 16 weeks after the last study agent administration. The study included males or females, ≥18 years of age, with active RA for 3 months from the onset of persistent synovitis. Subjects were allowed to be on a stable therapeutic regimen of up to two Disease Modifying Anti-Rheumatic Drugs (DMARDs), oral corticosteroids, and/or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), for the treatment of their RA. Intramuscular, intra-articular, and intravenous corticosteroids were not allowed within 4 weeks of study agent administration or for the duration of the study.

[4] ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

The study treatments were:

Stage I: placebo or golimumab at a dose of either 0.3 mg/kg, 0.6 mg/kg, 1.0 mg/kg, or 3.0 mg/kg, administered as a single dose. Subjects were followed for 16 weeks.

Stage II: placebo or golimumab 0.3 mg/kg or 1.0 mg/kg, each administered as three doses at 14 day intervals. Follow-up for 16 weeks after last study drug administration

A total of 53 subjects were included in the study: 29 subjects in Stage I and 24 different subjects in Stage II. In Stage II there were three males and 21 females with an age range of 18 to 81 years. Twenty nine subjects in Stage I received treatment, nine received placebo, five received 0.3 mg/kg, five received 0.6 mg/kg, five received 1.0 mg/kg, and five received 3.0 mg/kg. Twenty three subjects in Stage II received study treatment: nine received placebo, six received 0.3 mg/kg and eight received 1.0 mg/kg.

Plasma concentrations of TNF-α, IL-6, IL-1β, IL-8, MCP-1, VEGF, active transforming growth factor β (TGF-β1), sICAM-1, (pro)matrix metalloproteinase (MMP)-1, MMP-3, and annexin V and 7-amino actinomycin D (AAD) staining were measured. However, because there were low baseline values, and high variability these were not interpreted in the study.

In Stage II, a greater proportion of subjects achieved ACR 20 response in the golimumab 0.3 mg/kg (100.0%) and 1.0 mg/kg (80.0%) dose groups compared with placebo (60.0%). However, response appears to have been transitory. In Stage I, overall, 60.0%, 60.0%, 100.0%, and 100.0% of subjects in the 0.3 mg/kg, 0.6 mg/kg, 1.0 mg/kg, and 3.0 mg/kg golimumab dose groups, respectively, achieved an ACR 20 response at any time compared with 28.6% of subjects in the placebo group.

Study CP2006T-049 was an *in vitro* study of neutralizing antibody responses to golimumab in Study C0524T02 for nineteen enzyme immunoassay antibody positive patients who were administered golimumab subcutaneously. Study C0524T02 was a multicentre, randomised, double blind, placebo controlled, 5-arm dose ranging study in patients with RA. A bioassay was used that employed fixed concentrations of golimumab and TNF-α in the presence of TNF sensitive WEHI-C527 cells that die in the presence of TNF in a dose dependent manner. Subjects' serum was added to this system.

Study C0524T02 had included subjects with RA despite MTX therapy. The subjects had been dosed with golimumab 50 mg or 100 mg subcutaneously at 2 or 4 week intervals. Nineteen subjects had developed antibodies to golimumab and 28 individual serum samples from these subjects were tested. Of the 17 evaluable patients eight (47%) were positive for the presence of anti-golimumab neutralizing antibodies. Neutralizing antibody could not be detected for the remaining nine patients, but all of these patients had low titers (<1:40) in the enzyme immunoassay.

Study CP2007T-042 was an *in vitro* study to determine the domains of golimumab to which the anti-golimumab antibodies were directed. The study used samples from the 19 antibody positive patients in Study C0524T02. The study used a bridging ELISA, originally developed to confirm the specificity of antibodies to golimumab, which was adapted to determine the ability of: golimumab-Fc fragment, golimumab-Fab fragment, and a deglycosylated version of intact golimumab to inhibit the interaction between patient anti-drug antibodies and intact golimumab. Study C0524T02 included subjects with RA despite MTX therapy, and subjects positive for golimumab antibodies. The subjects had been treated with golimumab 50 mg or 100 mg subcutaneously at 2 or 4 week intervals. A total of 19 samples were tested but only 15 gave interpretable results. The signals due to patient antibody/golimumab interactions were inhibited (median percentage inhibition) by 76%, 81%, 78%, and 29% when the samples were preincubated with intact golimumab, deglycosylated golimumab, the Fab fragment, and the Fc fragment, respectively. These results indicated the anti-golimumab antibodies interacted with the Fab section of golimumab.

Evaluator's comments: The pharmacodynamic studies examined the effects of golimumab upon inflammatory markers, and the effects of golimumab at different doses upon efficacy measures for RA. The studies were dose finding studies used to direct the later efficacy studies in dose selection and outcome measures. The *in vitro* studies were useful in examining the nature of anti-golimumab antibodies. These antibodies were neutralizing and directed against the Fab portion of golimumab.

Efficacy

Efficacy data in subjects with ankylosing spondylitis

Study C0524T09-24wk GO-RAISE was a multicentre, randomised, double-blind, placebo controlled trial in patients with ankylosing spondylitis (AS). The study was conducted in 46 study centres: 20 in North America: US (11), Canada (9), 17 in Europe: Belgium (4), The Netherlands (2), Germany (8), Finland (2), and France (1), and 9 in Asia: South Korea (6), Taiwan (3). The study report covered the first 24 weeks for the study but the total intended duration of the study extension was 268 weeks. Inclusion and exclusion criteria are summarized in Table 2 below:

Table 2. Details of Study C0524T09-24wk GO-RAISE

Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation[5]	Results (efficacy)	Adverse Reactions
Multicentre, randomised, double-blind, placebo controlled trial in patients with ankylosing spondylitis	356 patients were randomised to treatment: 78 to placebo, 138 to golimumab 50 mg, and 140 to golimumab 100 mg 255 (71.6%) males and 101 (28.4%) females, age range 18 to 83 years At Week 16, 41 (52.6%) subjects in the placebo group switched to the golimumab 50 mg group and 25 (18.2%) in the 50 mg group switched to the 100 mg group	Women or men 18 years of age or older. Diagnosis of definite AS, as defined by the modified New York criteria, for at least 3 months prior to first administration of study agent. Both the radiographic criterion and at least one clinical criterion must be met: Have symptoms of active disease at screening and at baseline, as evidenced by both a BASDAI score of ≥4 and a VAS score for total back pain of ≥4, each on a scale of 0 to 10 cm. Either has an inadequate response to 3 months of continuous therapy with maximal recommended doses of NSAID(s), or is unable to receive a full 3 months of maximal NSAID therapy because of intolerance, toxicity, or contraindications to NSAIDs.	Full planned duration is 104 weeks Present report is for the first 24 weeks	1. Golimumab 50 mg 2. Golimumab 100 mg Subcutaneous injection at 4 week intervals	3. Placebo Randomised to placebo: golimumab 50 mg: golimumab 100 mg in a 1:1.8:1.8 ratio	The primary efficacy endpoint was ASAS 20 at Week 14. The major secondary efficacy endpoints were: ASAS 20 response at Week 24, change from baseline in functioning as measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14, and the change from baseline in mobility as measured by the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14.	ASAS 20, was achieved in more subjects in the golimumab groups, with similar efficacy for the two active treatment groups at Weeks 14 and 24. Similarly for BASFI there was greater efficacy in the golimumab groups, with similar efficacy for the two doses. More subjects in the golimumab treatment groups achieved low disease activity at Week 14.	Overall, AEs occurred to a similar extent in all treatment groups, but upper respiratory tract infection, elevated ALT, elevated AST, diarrhoea and headache occurred more frequently with golimumab. AEs were reported in 59 (76.6%) of subjects treated only with placebo and 255 (79.9%) of subjects who received golimumab. SAEs were reported in four (5.2%) subjects in the placebo group, five (3.6%) in the golimumab 50 mg and seven (5.0%) in the golimumab 100 mg. There were no deaths reported during the study One (1.3%) subject in the placebo group and 7 (2.5%) in the golimumab discontinued because of AEs 11 (3.5%) of patients treated with golimumab developed antibodies

[5] ASAS 20: A 20% improvement in response according to the criteria of the Assessment in Ankylosing Spondylitis (ASAS) International Working Group (ASAS 20) is defined as (1) an improvement of ≥20% from baseline and absolute improvement from baseline of at least 1 on a 0 to 10 cm scale in at least three of the following four domains - patient global, pin (total back pain), function (BASFI), inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness) and (2) absence of deterioration from baseline (≥20% and absolute change of at least 1 on a 0 to 10 cm scale) in the potential remaining domain. ASAS 40 is defined as a 40% improvement in 3 of 4 domains, with an absolute improvement of at least 2 on a 0 to 10 cm scale, and no deterioration in the remaining domain.

The study treatments were golimumab 50 mg, golimumab 100 mg or placebo.

Treatments were administered by subcutaneous injection at 4 week intervals. Subjects were randomised to placebo: golimumab 50 mg: golimumab 100 mg in a 1:1.8:1.8 ratio. Randomisation and allocation to treatment group was performed using an interactive voice response system. At Week 16 subjects in any group who had < 20% improvement from baseline in both total back pain and morning stiffness measures qualified to enter early escape in a double blinded fashion: placebo to golimumab 50 mg; and golimumab 50 mg to golimumab 100 mg. At Week 24 patients remaining in the placebo group were commenced on golimumab 50 mg.

The primary efficacy endpoint was ASAS 20 at Week 14. The secondary efficacy endpoints were: ASAS 20 response at Week 24, change from baseline in functioning as measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14, and the change from baseline in mobility as measured by the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14.[6,7] Hypothesis tests were performed using Pearson's chi-square test, Cochran-Mantel-Haenszel chi-square test and ANOVA.

A total of 356 patients were randomised to treatment: 78 to placebo, 138 to golimumab 50 mg, and 140 to golimumab 100 mg. The study groups were similar in baseline demographics and disease severity. Of the randomised subjects, there were 255 (71.6%) males and 101 (28.4%) females, with an age range of 18 to 83 years. At Week 16, 41 (52.6%) subjects in the placebo group switched to the golimumab 50 mg group and 25 (18.2%) in the 50 mg group switched to the golimumab 100 mg group. Two (2.6%) subjects in the placebo group, nine (6.5%) in the golimumab 50 mg and four (2.9%) in the golimumab 100 mg withdrew from the study.

The primary efficacy outcome measure, ASAS 20, occurred in significantly more subjects in the golimumab groups, with similar efficacy for the two active treatment groups at Weeks 14 and 24. Similarly for BASFI there was greater efficacy in the golimumab groups, with similar efficacy for the two doses. There were no significant changes in BASMI at either Week 14 or Week 24. More subjects in the golimumab treatment groups achieved low disease activity at Week 14. The improvement in ASAS 20 occurred from week 4 and was maintained through to Week 24. BASDAI and global disease activity score improved to a similar extent in both golimumab groups. There was a significant increased in chest expansion in the golimumab 50 mg group: mean (SD) 0.55 (1.491) cm, p=0.013 at Week 24. At Week 24 haemoglobin levels did not change in the placebo group but there was a mean (SD) increase in the golimumab 50 mg group of 1.153 (1.0096)

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[6] Bath Ankylosing Spondylitis Functional Index (BASFI). A BASFI response is represented as a mean (VAS; 0 to 10 cm) of 10 questions, 8 of which relate to the functional anatomy of subjects and 2 of which relate to a subject's ability to cope with everyday life

[7] Bath Ankylosing Spondylitis Metrology Index Scoring System (BASMI)

	Score		
Measurement	0	1	2
1. Tragus-to-wall	< 15 cm	15 to 30 cm	> 30 cm
2. Lumbar flexion (Schober test)	> 4 cm	2 to 4 cm	< 2 cm
3. Cervical rotation	> 70°	20 to 70°	< 20°
4. Lumbar side flexion	> 10 cm	5 to 10 cm	< 5 cm
5. Intermalleolar distance	> 100 cm	70 to 100 cm	< 70 cm

g/dL and in the 100 mg group of 1.830 (0.7908) g/dL. Quality of life score (SF-36) and Jenkins sleep assessment both improved in the golimumab groups compared with placebo. There was no difference between the groups in time lost from work or employability, but at weeks 16 and 24 change in productivity was better in the golimumab groups than the placebo ($p<0.001$).

Decreases in MMP-3 were observed at Week 14 for both golimumab 50 mg: 15.95% and golimumab 100 mg: 17.6% ($p < 0.001$) while a greater increase from baseline was observed for the placebo group. At Week 14 there were significant decreases from baseline in ICAM-1 for golimumab 100 mg: 9.05%; and golimumab 50 mg: 8.95% compared to the placebo group($p < 0.001$). Decreases in IL-6 levels were noted following treatment with golimumab 50 mg: 57.1% and 100 mg: 59.1% compared to placebo ($p < 0.001$). At Week 4 there were decreases in VEGF in the golimumab 50 mg (35.9%) and golimumab 100 mg (29.9%) groups compared to placebo ($p < 0.001$). TNF-α concentrations decreased over time in a dose dependent manner, with decreases of 15.9% and 20.9% in golimumab 50 mg and 100 mg groups respectively at Week 4 as compared to the placebo group ($p < 0.003$). TNF-α decreased by 44.9% and 60% for golimumab 50 mg and 100 mg respectively at Week 14 ($p < 0.001$). A significant increase in osteocalcin was observed in the combined golimumab group compared to placebo at Week 4 ($p = 0.028$). PINP increased at Week 4 in the golimumab 50 mg (15%) and 100 mg (13.1%) groups compared to placebo ($p < 0.001$).

Studies conducted in subjects with psoriatic arthritis

Study C0524T08-24wk GO-REVEAL was a multicentre, randomised, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab in adult subjects with active psoriatic arthritis. The study was conducted at 58 centres: 36 in North America: US (18), Canada (18); 22 in Europe: Belgium (5), Poland (10), Spain (3) and UK (4). The first 24 weeks (placebo controlled phase) of the study is reported, with the total intended duration of the study (extension phase) being 268 weeks. Inclusion and exclusion criteria are summarized in Table 3 below:

Table 3. Details of Study C0524T08-24wk GO-REVEAL

Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
multicentre, randomised, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab in adult subjects with active psoriatic arthritis.	405 subjects were randomised to treatment: 113 to placebo, 146 to golimumab 50 mg and 146 to golimumab 100 mg. There were 244 (60.2%) male subjects, 161 (39.8%) female and the age range was 20 to 78 years. The treatment groups were similar in demographic characteristics, disease duration and baseline disease	Women or men 18 years of age or older. Psoriatic arthritis that was diagnosed at least 6 months prior to the first administration of study agent. Active Psoriatic Arthritis at the time of screening and at baseline, as characterized by 3 or more swollen joints and 3 or more tender joints. At least one of	Up to 52 weeks, 24 week covered by the submitted report Placebo controlled through to 24 weeks Total duration of treatment up to 48 weeks with follow-up to 52	1. golimumab 50 mg 2. golimumab 100 mg Treatments were administered subcutaneously every 4 weeks Randomised using an interactive voice response system	3. placebo Subjects were randomly assigned in a 1:1.3:1.3 ratio At Week 16, subjects with <10% improvement from baseline in SJC and TJC could move from placebo to 50 mg and from 50 mg to 100 mg	the primary efficacy endpoint was American College of Rheumatology (ACR) 20 response at Week 14. Secondary efficacy endpoints were: ACR 20 response at Week 24, Psoriasis Area and Severity Index (PASI) 75 response at Week 14 in a subset of subjects with ¡Ý 3% body surface area (BSA)	For ACR 20there was greater efficacy for golimumab than placebo, and a plateau of effect at the 50 mg level. PASI 75 response was also significantly better in the golimumab groups There was a significant improvement in HAQ score at Week 24 for both golimumab groups compared to	The overall rate of AEs was higher in the golimumab groups at 64.7%, than in the placebo group at 59.3%. No deaths were reported during the 24 week study period. SAEs were reported in six (5.3%) subjects in the placebo group, three (2.1%) in the golimumab

	characteristics	the Psoriatic Athritis subsets: DIP joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. Active plaque psoriasis with a qualifying target lesion ≥2 cm in diameter, but not on axilla, inframammary area, or groin. Active arthritis despite current or previous DMARD or NSAID therapy	weeks			psoriasis skin involvement at baseline, improvement from baseline in HAQ scores at Week 24, and change from baseline in the physical component summary score of the SF 36 at Week 14.	both baseline and placebo. There was a significant improvement in the SF-36 physical component summary scores at Week 14 for both golimumab groups compared to baseline and placebo. There were similar improvements in ACR 50 and ACR 70. There were reductions in the number of swollen and tender joints in both golimumab groups compared to baseline and placebo from Week 4, persisting through to Week 24	50 mg, and two (1.4%) in the golimumab 100 mg. Infections were reported in 23 (20.4%) subjects in the placebo group, 36 (24.7%) in the golimumab 50 mg and 39 (26.7%) in the golimumab 100 mg. 4 (3.5%) subjects in the placebo group, 2 (1.4%) in the golimumab 50 mg and 2 (1.4%) in the golimumab 100 mg discontinued because of an AE. 13 (3.9%) of all subjects treated with golimumab developed antibodies

The study treatments were golimumab 50 mg, golimumab 100 mg or placebo.

Treatments were administered subcutaneously every 4 weeks. Subjects were randomly assigned in a 1:1.3:1.3 ratio to placebo:golimumab 50mg:golimumab 100mg. At Week 16, subjects with <10% improvement from baseline in SJC and TJC could move from placebo to 50 mg and from 50 mg to 100 mg. Subjects were randomised using an interactive voice response system. Treatment duration was planned for up to 52 weeks, but only the first 24 weeks are covered by the submitted report. The study was placebo controlled through to 24 weeks, with total duration of treatment up to 48 weeks and follow-up to 52 weeks. At Week 24 patients remaining in the placebo group were commenced on golimumab 50 mg.

The primary efficacy endpoint was ACR 20 response at Week 14. Definitions of the outcome measures are provided in were provided. Secondary efficacy endpoints were: ACR 20 response at Week 24, Psoriasis Area and Severity Index (PASI) 75 response at Week 14 in a subset of subjects with ≥3% body surface area (BSA) psoriasis skin involvement at baseline; improvement from baseline in health assessment questionnaire (HAQ) scores at Week 24; and change from baseline in the physical component summary score of the SF 36 at Week 14. Hypothesis tests were performed using Pearson's chi-square test, Cochran-Mantel-Haenszel chi-square test and ANOVA.

A total of 405 subjects were randomised to treatment: 113 to placebo, 146 to golimumab 50 mg and 146 to golimumab 100 mg. There were 244 (60.2%) male subjects, 161 (39.8%) female and the age range was 20 to 78 years. The treatment groups were similar in demographic characteristics, disease duration and baseline disease characteristics. Fifty one (45.1%) subjects in the placebo

group transferred to the golimumab 50 mg group at Week 16, and 28 (19.2%) subjects from the golimumab 50 mg group transferred to the golimumab 100 mg group. Ten (8.8%) subjects in the placebo group, seven (4.8%) in the golimumab 50 mg and two (1.4%) in the golimumab 100 mg group discontinued. Four (3.5%) subjects in the placebo group, two (1.4%) in the golimumab 50 mg and two (1.4%) in the golimumab 100 mg discontinued because of an AE.

For the primary efficacy outcome measure, there was greater efficacy for golimumab than placebo, and a plateau of effect at the 50 mg level. The improvement in ACR 20 response was maintained through to Week 24. PASI 75 response was also significantly better in the golimumab groups: 40.4% for golimumab 50 mg, 58.3% for golimumab 100 mg and 2.5% for placebo ($p<0.001$). There was a significant improvement in HAQ score at Week 24 for both golimumab groups compared to both baseline and placebo. There was a significant improvement in the SF-36 physical component summary scores at Week 14 for both golimumab groups compared to baseline and placebo. There were similar improvements in ACR 50 and ACR 70. There were reductions in the number of swollen and tender joints in both golimumab groups compared to baseline and placebo from Week 4, persisting through to Week 24. There was an improvement in CRP from baseline and compared to placebo in the golimumab groups from Week 4 and persisting through to Week 24. There were more DAS28 responders in the golimumab groups than for placebo from Week 4 through to Week 24. Morning stiffness decreased from baseline, and compared to placebo for both golimumab groups from Week 4 and persisting through to Week 24. There were fewer subjects with dactylitis and enthesitis in the golimumab groups than placebo at Weeks 14 and 24. There was an increase in mean haemoglobin levels in both golimumab groups by Week 24: mean (SD) increase 1.005 (0.9658) for 50 mg and 1.729 (1.6680) for 100 mg.

In comparison with placebo and baseline, in the golimumab groups there was a significant decrease in MMP-3 and IL-8 at Weeks 4 and 14; decrease in ICAM-1, IL-6, and VEGF from Weeks 4 to 24; and TNF-α at Week 14. In comparison with placebo and baseline, in the golimumab groups there was a significant increase in osteocalcin and PINP at Week 4. In comparison with placebo and baseline, in the golimumab groups there was a significant decrease in DPD. There was no significant difference between the groups in BAP or clinically significant difference in PYD.

Studies conducted in patients with rheumatoid arthritis

Study C0524T02 was a multicentre, randomised, double-blind, dose-ranging, placebo controlled study of golimumab subcutaneous injection in subjects with active rheumatoid arthritis despite treatment with methotrexate. The study was an add-on treatment study conducted on patients treated with MTX. The study was conducted at 40 study centres: 19 in North America: US (13), Canada (6), 14 in Europe: Belgium (5), UK (4), Germany (5); 7 in Australia. Inclusion and exclusion criteria are summarized in Table 4 below:

Table 4. Details of Study C0524T02

Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Multicentre, randomised, double-blind, dose-ranging, placebo controlled study of golimumab subcutaneous injection in subjects with active rheumatoid arthritis despite treatment with methotrexate	172 subjects were randomised to treatment 132 (76.7%) female and 40 (23.3%) male Age range 23 to 83 years The treatment groups were similar in demographic characteristics, baseline disease severity and duration	Men and women 18 years of age or older For at least 3 months prior to screening, they had a diagnosis of RA (as defined by ACR) Active RA despite MTX therapy No previous anti-TNF α therapy treatment Subjects must have tolerated MTX at a dose of at least 10 mg/week for at least 3 months prior to being treated with their first dose of study drug. Subjects on stable, low doses of oral corticosteroids (not exceeding the equivalent of 10 mg of prednisone per day) and marketed NSAIDs were eligible for enrollment. No evidence of active or latent TB on TB screening.	Golimumab 50 mg every 2 weeks Golimumab 50 mg every 4 weeks Golimumab 100 mg every 2 weeks Golimumab 100 mg every 4 weeks Up to Week 20; then all treatments were administered every 4 weeks through to Week 48 Randomization was in an equal proportion to study group and stratified by study centre Allocation to treatment group using interactive voice response system	Placebo SC injections at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, and 18 Infliximab 3 mg/kg IV infusions at Weeks 20, 22, 28 and then every eight weeks through to Week 44	The primary efficacy outcome measure was ACR 20 response at Week 16. The analysis was intention to treat. Secondary efficacy outcome measures were: ACRn , ACR 50 and ACR 70 at Week 16; improvement in SJC and TJC through to Week 52; DAS 28 at Week 16; Hypothesis testing using chi^2 test and ANOVA	For the primary outcome measure (ACR 20 response at Week 16) there was a significant difference between golimumab 100 mg very 2 weeks compared to placebo but not for the other treatment groups Except for the 50 mg very 2 week group, for ACRn golimumab was superior to placebo, with no apparent difference between 50 mg every 4 weeks and 100 mg every 2 weeks. For ACR 50 and ACR 70, golimumab was superior to placebo overall, but with no apparent dose effects For DAS 28 response, the golimumab 100 mg every 2 weeks group demonstrated the greatest efficacy	At Week 20, 29 (85%) subjects in the placebo and 118 (86.1%) in the golimumab groups reported AEs. Up to Week 52, 29 (85.3%) subjectsin the placebo, 16 (64.0%) in the infliximab and 130 (94.9%) in the golimumab reported AEs. One subject died 4 months after last administration of golimumab. Prior to Week 20, 3 (8.6%) subjects in the placebo group and 9 (6.6%) in the golimumab discontinued because of AEs. To Week 52, 6 (17.1%) in the placebo/infliximab group and 16 (9.3%) in the golimumab discontinued because of AEs. 9 (8.2%) of subjects developed antibodies to golimumab through to Week 52, 19 (17.3%) developed antibodies through to Week 68

The study treatments were golimumab 50 mg every 2 weeks, golimumab 50 mg every 4 weeks, golimumab 100 mg every 2 weeks, golimumab 100 mg every 4 weeks or placebo SC injections at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, and 18, followed by Infliximab 3 mg/kg IV infusions at Weeks 20, 22, 28 and then every eight weeks through to Week 44.

From Week 20 all golimumab treatments were administered every 4 weeks through to Week 48. Randomization was in an equal proportion to study group and stratified by study centre. Allocation to treatment group was performed using an interactive voice response system. There was no allowance for early escape.

The primary efficacy outcome measure was ACR 20 response at Week 16. The analysis was intention to treat. Secondary efficacy outcome measures were: ACRn, ACR 50 and ACR 70 at Week 16; improvement in SJC and TJC through to Week 52; DAS 28 at Week 16; Hypothesis tests were performed using the chi^2 test and ANOVA.

A total of 172 subjects were randomised to treatment. Of the randomised subjects, 132 (76.7%) female and 40 (23.3%) male, and the age range was 23 to 83 years. The treatment groups were similar in demographic characteristics, baseline disease severity and duration. For the primary outcome measure (ACR 20 response at Week 16) there was a significant difference between golimumab 100 mg every 2 weeks compared to placebo but not for the other treatment groups. Interestingly, in the subgroup of patients recruited from Australia there was no difference between the placebo group and golimumab in ACR 20 response: 5 (60.0%) subjects for placebo and 27 (55.6%) for golimumab p=0.854. The ACR 20 response was maintained through to Week 52. Except for the 50 mg every 2 week group, for ACRn golimumab was superior to placebo, with no apparent difference between 50 mg every 4 weeks and 100 mg every 2 weeks. For ACR 50 and ACR 70, golimumab was superior to placebo overall, but with no apparent dose effects. For DAS 28 response, the golimumab 100 mg every 2 weeks group demonstrated the greatest efficacy.[8]

In the golimumab treatment groups there was a decrease in plasma concentrations of inflammatory markers: IL-6 decreased from baseline by 23.9% to 52.2%, VEGF decreased by 18.9% to 46.8%, IL-8 decreased by 17% to 31.3%, IL-18 decreased by 3.4% to 22%, intercellular adhesion molecule-1 (ICAM-1) decreased by 12.1% to 19.5%, MMP-1 decreased by 16.3% to 38.9%, MMP-3 decreased by 18.5% to 29.8%, MMP-9 decreased by 13.3% to 37.2%, MMP-13 decreased by 13.7% to 20.1%, tissue inhibitor of metalloproteinase (TIMP-1) decreased by 8.5% to 29.7%, A-SAA decreased by 42.3% to 73.4%, and E-selectin decreased by 21.1% to 38.4%. There was no apparent change in TNF-α. In the placebo group there was little change in inflammatory markers. With regard to serum levels of markers of cartilage turnover, in the golimumab groups there was a decrease in osteoprotegerin decrease by 12.7% to 32.5%, but no apparent differences from placebo in receptor activator of NF-kappaB ligand or COL 2-3/4C long neoepitope.

Study C0524T05-24wk GO-BEFORE was a multicentre, randomised, double-blind, comparator-controlled, 4-arm, parallel-group study of golimumab alone or in combination with MTX in MTX-naïve subjects who had RA for at least 3 months prior to randomization. The study was conducted at 90 centres: Asia – 25 sites: India (3), Malaysia (3), Philippines (5), Singapore (1), Republic of Korea (5), Taiwan (4), Thailand (4); Europe/Australia/New Zealand – 34 sites: Australia (2), Austria (1), Belgium (2), Hungary (3), Italy (1), New Zealand (3), Poland (7), Russia (4), Spain (5), Ukraine (4), UK (2); Latin America – 10 sites: Argentina (7), Chile (3); North America – 21 sites: Canada (3), US (18). The results of the first 24 weeks of the study are presented in the report, with the remaining double blind phase (to Week 52) and long-term extension phase (to Week 268) to be reported later. Inclusion and exclusion criteria are summarized in Table 5 below:

[8] DAS28 response:

	Improvement in DAS28 score		
Present DAS28 score	> 1.2	> 0.6 to ≤ 1.2	≤ 0.6
≤ 3.2	Good response	Moderate response	No response
> 3.2 to ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

Table 5. Details of Study C0524T05-24wk GO-BEFORE

Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Multicentre, randomised, double-blind, comparator-controlled, 4-arm, parallel-group study of golimumab alone or in combination with MTX in MTX-naïve subjects who had RA for at least 3 months prior to randomization.	637 randomised and 634 treated. Of the randomised subjects, 528 (82.9%) were female and 109 (17.1%) were male, age range 18 to 85 Randomised/treated subjects in each groups were: Placebo + MTX – 160/160; Golimumab 100 mg + placebo – 159/157; Golimumab 50 mg + MTX – 159/158; Golimumab 100 mg + MTX – 159/159.	Men and women 18 years of age or older Diagnosis of RA for at least 3 months before the first administration of study agent, Methotrexate (MTX)-naïve (had not received more than 3 weekly doses of MTX for RA at any time) Active RA as defined by persistent disease activity with at least four swollen and four tender joints at the time of screening and baseline and met at least two of the following four criteria: 1. CRP ≥1.5 mg/dL at screening or ESR ≥28 mm in the first hour at screening or baseline; 2. Morning stiffness of ≥30 minutes at screening and baseline ; 3. Bone erosion by x-ray and/or MRI prior to first administration of study agent; 4. anti-CCP antibody-positive or rheumatoid factor positive at screening	1. Golimumab 100 mg plus placebo 2. Golimumab 50 mg plus MTX 3. Golimumab 100 mg plus MTX Golimumab was administered by subcutaneous injection every 4 weeks beginning at Week 0. MTX was administered orally at a dose of 10 mg/week starting at Week 0, with a dose escalation to 20 mg/week by Week 8.	4. Placebo plus MTX Randomised using interactive voice response system, stratified by study site Randomised to study group in equal proportions All study subjects received at least 5 mg folic acid or oral folinic acid weekly	The primary efficacy outcome measures were: Proportion of subjects achieving ACR 50 response at Week 24, Secondary efficacy outcome measures were: ACR 20 response at Week 24, ACR 50 response at Week 24 in subjects with abnormal CRP at baseline; ACR 70; ACR 90,; ACR-N; DAS 28 Healthcare utilization, time lost from work, and changes in employability and self reported productivity were assessed at Week 24.	Although greater proportions of subjects achieved ACR 50 response in the golimumab groups, the differences were not statistically significant Non-inferiority testing was performed as a secondary analysis between golimumab 100 mg + placebo and placebo + MTX, using a difference of -10% as the criteria for non-inferiority, and the lower bound of the 95% CI for the difference in ACR 50 response at Week 24 between these groups was –5.2%. This was interpreted as demonstrating non-inferiority. There were no apparent differences between the dose groups of golimumab. For ACR 20, there was no significant difference between golimumab 100 mg and MTX, but both golimumab + MTX groups were superior to MTX alone.	AEs were reported in 116 (72.5%) in the MTX group, 107 (68.2%) in the golimumab 100 mg, 129 (81.6%) in the golimumab 50 mg + MTX and 121 (76.1%) in the golimumab 100 mg + MTX. Two subjects died during the 24 week study period: The number (%) of subjects with at least one SAE was 11 (6.9%) in the MTX group, 5 (3.2%) in the golimumab 100 mg, 10 (6.3%) in the golimumab 50 mg + MTX and 10 (6.3%) in the golimumab 100 mg + MTX. Discontinuations because of AEs occurred in 1 (0.6%) subject in the MTX group, one (0.6%) in the golimumab 100 mg, 5 (3.1%) in the golimumab 50 mg + MTX and 6 (3.8%) in the golimumab 100mg + MTX. 20 (6.3%) subjects developed antibodies

The study treatments were golimumab 100 mg plus placebo, golimumab 50 mg plus MTX, golimumab 100 mg plus MTX or placebo plus MTX.

Subjects were randomised using interactive voice response system, and stratified by study site. Subjects were randomised to study group in equal proportions. All study subjects received at least 5 mg folic acid or oral folinic acid weekly. Golimumab was administered by subcutaneous injection every 4 weeks beginning at Week 0. MTX was administered orally at a dose of 10 mg/week starting at Week 0, with a dose escalation to 20 mg/week by Week 8. At Week 28, any subject who has < 20% improvement from baseline in both SJC and TJC entered early escape in a double-blinded fashion: placebo + MTX to golimumab 50 mg + MTX; golimumab 100 mg + placebo to golimumab 100 mg + MTX; and golimumab 50 mg + MTX to golimumab 100 mg + MTX.

The primary efficacy outcome measure was the proportion of subjects achieving ACR 50 response at Week 24. Secondary efficacy outcome measures were: ACR 20 response at Week 24, ACR 50 response at Week 24 in subjects with abnormal CRP at baseline; ACR 70; ACR 90; ACR-N; DAS 28; healthcare utilization; time lost from work; and changes in employability and self reported productivity, assessed at Week 24.[9]

A total of 637 subjects were randomised and 634 received study treatment. Of the randomised subjects, 528 (82.9%) were female and 109 (17.1%) were male, and the age range was 18 to 85 years. Randomised/treated subjects in each groups were: Placebo + MTX – 160/160; Golimumab 100 mg + placebo – 159/157; Golimumab 50 mg + MTX – 159/158; Golimumab 100 mg + MTX – 159/159. Treatment groups were similar in baseline demographic, disease severity and duration.

Although greater proportions of subjects achieved ACR 50 response in the golimumab groups, the differences were not statistically significant. Non-inferiority testing was performed as a secondary analysis between golimumab 100 mg + placebo and placebo + MTX, using a difference of -10% as the criteria for non-inferiority, and the lower bound of the 95% CI for the difference in ACR 50 response at Week 24 between these groups was –5.2%. This was interpreted as demonstrating non-inferiority. There were no apparent differences between the dose groups of golimumab. In the proportion of subjects achieving ACR 20, there was no significant difference between golimumab 100 mg and MTX, but both golimumab + MTX groups were superior to MTX alone. There was no significant difference between the groups in the proportion of subjects with abnormal baseline CRP who achieved an ACR 50 response at Week 24. At each time point ACR 20, ACR 50, ACR 70 and ACR 90 responses were similar for the golimumab 100 mg alone and MTX alone groups. The responses were also similar for the golimumab 50 mg + MTX and golimumab 100 mg + MTX groups. ACR-N improved for all the groups over time, but there were no significant differences between the groups. CRP also improved for all groups over time but there were no significant differences between the groups. For DAS 28, there was no significant difference between golimumab alone and MTX alone, but the combined golimumab + MTX group was superior to MTX alone. There were no significant differences between the groups in the change from baseline in SF-36 physical component summary scores at Week 24. Similarly there were no differences between the groups in SF-36 mental component scores. There were no differences between the groups in resource utilization, time lost from work, change from baseline in employability or change from baseline in productivity. There was less time lost from work for caregivers in the golimumab 100 mg + MTX group than the MTX alone group (p=0.03).

[9] ACR-N: ACR-N was defined as the minimum of the following three: (1) the percentage improvement from baseline in tender joint counts (68 joints), (2) the percentage improvement from baseline in swollen joint counts (66 joints) and (3) the median percentage improvement from baseline for the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), evaluator's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ, CRP.

Across all treatment groups, serum levels of markers of inflammation decreased from baseline by Week 4. Treatment in the combined golimumab + MTX group significantly reduced serum levels of MMP-3, ICAM-1, IL-6, and VEGF at Week 4, and ICAM-1, IL-6, VEGF, TNF-α, IL-8, and RF at Week 24 when compared with placebo + MTX. Compared with the placebo + MTX treatment group, the changes in serum marker levels of bone and cartilage metabolism (bone alkaline phosphatase, Osteocalcin, N-terminal propeptide of type I procollagen, pyridinoline, deoxypyridinoline, COL 2-3/4C and hyaluronic acid) were not significantly different from those in the combined golimumab + MTX group.

In the combined golimumab + MTX group, fibrinogen and IL-6 decreased to a greater extent than MTX alone. IL-8 and ICAM-1 decreased to a greater extent in all the golimumab groups than MTX alone. For the remaining markers of cardiovascular safety there were no significant differences between the treatment groups: MMP-3, VEGF, hsCRP, amyloid A, homocysteine, adiponectin, triglycerides, total cholesterol, LDL, HDL, total cholesterol/HDL, LDL/HDL, apolipoprotein A1, apolipoprotein B, apolipoprotein B/apolipoprotein A1, total LDL particles, IDL, large LDL, total small LDL, medium small LDL, very small LDL, mean LDL size, glucose, insulin, HbA1c, G/I ratio, HOMA-IR, HOMA-%β-cell, and QUICKI.

Study C0524T-06-24wk was a multicentre, randomised, double-blind, placebo-controlled, four parallel group study of the efficacy and safety of golimumab 50 mg or 100 mg plus methotrexate (MTX) compared with placebo + MTX, and golimumab 100 mg + placebo compared with placebo + MTX in subjects with active Rheumatoid Arthritis (RA) despite prior MTX therapy. There were 60 sites in twelve countries: including Argentina (9), Australia (3), Canada (6), Chile (4), Germany (6), Hungary (1), Mexico (1), New Zealand (3), Poland (6), South Korea (6), Taiwan (1), and US (12). The data for the first 24 weeks of the study are presented in the report, with further data to 52 weeks, and long-term extension data to Week 268 to be submitted at a later date by the sponsor. Inclusion and exclusion criteria are summarized in Table 6 below:

Table 6. Details of Study C0524T-06-24wk

Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Multicentre, randomised, double-blind, placebo-controlled study of the efficacy and safety of golimumab 50 mg or 100 mg plus MTX compared with placebo + MTX, and golimumab 100 mg + placebo compared with placebo + MTX in subjects with active RA despite MTX therapy.	A total of 444 subjects were randomised to treatment: 133 to MTX, 133 to golimumab 100 mg, 89 to golimumab 50 mg + MTX and 89 to golimumab 100 mg + MTX. 358 (80.6%)were female and 86 (19.4%) were male age range 18 to 79 years The treatment groups were similar in demographics, baseline disease severity and duration	Males or females 18 years of age or older Diagnosis of RA for at least 3 months prior to screening Active RA despite MTX therapy, defined as: persistent disease activity that on a stable dose of at least 15 mg/week (and ≤25 mg/week) of MTX for at least 4 weeks prior to screening and had at least 4 swollen and 4 tender joints and at least 2 of the following 4 criteria: 1. C-reactive protein (CRP) ≥1.5 mg/dL at screening or ESR by Westergren method of ≥28 mm in the first hour at screening or baseline; 2. Morning stiffness of ≥30 minutes at screening and baseline; 3. Bone erosion by x-ray and/or MRI prior to first administration of study agent; 4. anti-CCP positive or RF-positive at screening	1, golimumab 100 mg + placebo for MTX 2. golimumab 50 mg + MTX 3. golimumab 100 mg + MTX Golimumab administered by subcutaneous injection at 4 week intervals Randomisation by interactive voice response system All subjects received at least 5 mg oral folic acid or oral folinic acid weekly during the blinded period	4. MTX + placebo for golimumab randomly assigned in a 3:3:2:2 ratio to MTX: golimumab: golimumab 50 mg + MTX: golimumab 100 mg + MTX At Week 16, any subject who had < 20% improvement from baseline in both swollen and tender joint count was to enter early escape in a double-blinded fashion.	The primary efficacy outcome measures were: ACR 20 response at Week 14 and the improvement from baseline in HAQ at Week 24 Secondary efficacy outcome measures were: improvement from baseline in van der Heijde Modified Sharp (vdH-S) score at Week 24; proportion of subjects with DAS28 (using CRP) response at Week 14; proportion of subjects with an ACR 20 response at Week 24: improvement from baseline in HAQ at Week 14 Hypothesis testing using the chi-square test and ANOVA	Significantly more subjects in the golimumab + MTX groups achieved ACR 20 than in the MTX alone group, but the difference between golimumab alone and MTX alone did not reach statistical significance. For HAQ score at Week 24, golimumab + MTX was superior to MTX, but there was no significant difference between MTX and golimumab alone. There was a similar result for HAQ at Week 14. There were more DAS 20 responders in the golimumab + MTX groups than the MTX group alone, but no significant difference between MTX and golimumab alone. There were more ACR 20 responders at Week 24 in the golimumab + MTX groups than the MTX group alone, but no significant difference between MTX and golimumab alone	AEs were reported in 90 (67.7%) subjects who were treated with MTX alone, 93 (69.9%) treated with golimumab alone and 174 (68.2%) treated with golimumab + MTX. Upper respiratory tract infections were the most common AE in all the treatment groups. SAEs occurred in 3 (2.3%) subjects in the MTX group, 5 (3.8%) in the golimumab, 5 (5.6%) in the golimumab 50 mg + MTX and 8 (9.0%) in the golimumab 100 mg + MTX. One or more serious infections occurred in 1 (0.8%) subjects in the MTX group, 3 (2.3%) in the golimumab and 8 (3.1%) in the golimumab + MTX. One patient in the golimumab alone group died from sepsis. 3 (1.5%) golimumab treated subjects developed antibodies

The study treatments were golimumab 100 mg + placebo for MTX, golimumab 50 mg + MTX, golimumab 100 mg + MTX or MTX + placebo for golimumab.

Subjects were randomly assigned in a 3:3:2:2 ratio to MTX: golimumab: golimumab 50 mg + MTX: golimumab 100 mg + MTX. Golimumab was administered by subcutaneous injection at 4 week intervals. MTX was administered orally at a dose of 2.5 mg per day. Randomisation was performed by interactive voice response system. All subjects received at least 5 mg oral folic acid

or oral folinic acid weekly during the blinded period. At Week 16, any subject who had < 20% improvement from baseline in both swollen and tender joint count was to enter early escape in a double-blinded fashion: placebo + MTX to golimumab 50 mg + MTX; golimumab 100 mg + placebo to golimumab 100 mg + MTX; and golimumab 50 mg + MTX to golimumab 100 mg + MTX. At week 24, the subjects in the placebo + MTX group all moved to the golimumab 50 mg + MTX treatment.

The primary efficacy outcome measures were: ACR 20 response at Week 14 and the improvement from baseline in HAQ at Week 24. Secondary efficacy outcome measures were:

- Improvement from baseline in van der Heijde Modified Sharp (vdH-S) score at Week 24
- Proportion of subjects with DAS28 (using CRP) response at Week 14
- Proportion of subjects with an ACR 20 response at Week 24
- Improvement from baseline in HAQ at Week 14
- ACR-N index of improvement at Weeks 14 and 24
- Proportion of subjects with DAS28 (using CRP and/or ESR) response at Week 24
- Proportion of subjects in DAS28 remission at Weeks 14 and 24
- Change from baseline in DAS28 (using CRP and/or ESR)
- Proportion of subjects achieving an ACR 20, 50, 70, and 90 responses
- Improvement from baseline in HAQ over time

Hypothesis tests were performed using the chi-square test and ANOVA.

A total of 444 subjects were randomised to treatment: 133 to MTX, 133 to golimumab 100 mg, 89 to golimumab 50 mg + MTX and 89 to golimumab 100 mg + MTX. Of the randomised subjects, 358 (80.6%) were female, 86 (19.4%) were male and the age range was 18 to 79 years. The treatment groups were similar in demographics, baseline disease severity and duration. Ten (7.5%) subjects in the MTX group discontinued subcutaneous treatment, compared with nine (6.8%) for golimumab, two (2.2%) for golimumab 50 mg + MTX and seven (7.9%) for golimumab 100 mg + MTX.

Significantly more subjects in the golimumab + MTX groups achieved ACR 20 than in the MTX alone group, but the difference between golimumab alone and MTX alone did not reach statistical significance. For HAQ score at Week 24, golimumab + MTX was superior to MTX, but there was no significant difference between MTX and golimumab alone. There was a similar result for HAQ at Week 14. Data on the change from baseline in vdH-S score at Week 24 was not provided in the report. There were more DAS 20 responders in the golimumab + MTX groups than the MTX group alone, but no significant difference between MTX and golimumab alone. There were more ACR 20 responders at Week 24 in the golimumab + MTX groups than the MTX group alone, but no significant difference between MTX and golimumab alone. For ACR 50 and ACR 70, golimumab + MTX was superior to MTX alone, but there was no difference between the groups in ACR 90. For all the outcome measures there was no apparent difference between golimumab 50 mg + MTX and golimumab 100 mg + MTX, but hypothesis testing was not performed between these two treatment groups. At Week 14 ACR-N, DAS 28 (using ESR), and SF-36 physical component summary scores improved to a greater extent in all golimumab groups, but at Week 24 there was no significant difference between golimumab alone and MTX alone. At Week 24, the median change from baseline in the SF-36 mental component summary scores was greater in the combined golimumab + MTX group than in the placebo + MTX group: mean (SD) 3.07 (10.81) and 0.75 (9.676) respectively, p=0.045. There was a greater change from baseline in functional assessment of chronic illness therapy-fatigue (FACIT-F) at Week 14 and Week 24 for all the golimumab groups compared to MTX alone. At Week 14, BPI pain severity score improved to a greater extent in the golimumab + MTX group than MTX alone. There was a significantly greater improvement in haemoglobin levels in the golimumab + MTX groups than MTX alone at both Week 14 and Week 24. At Week 14, there were decreases in total cholesterol, HDL and LDL in the golimumab

+ MTX groups relative to MTX alone. Homocysteine decreased in the golimumab alone group compared with MTX alone at Week 14: mean (SD) -1.367 ± (2.5723) for golimumab and -0.051 (2.4535) for MTX $p<0.001$. At Week 24, fibrinogen IL-6, ICAM-1, MMP-3, VEGF, hsCRP and amyloid A all decreased in the golimumab + MTX groups relative to MTX alone. There were no significant differences in healthcare utilisation, time lost from work by subjects or caregivers, or employability between the treatment groups, except for time lost from work being lower for the golimumab 50 mg + MTX compared with MTX at Week 24 ($p=0.045$). At Week 24, there was an improvement from baseline in self-reported productivity in the combined golimumab + MTX group compared with MTX: median change -1.900 compared with -0.400, $p<0.001$).

There were significant decreases at Week 4 and Week 14 in MMP-3, ICAM-1, IL-6, and VEGF in the combined golimumab + MTX group compared with the placebo + MTX. There was a statistically significant decrease in RF levels in the combined golimumab + MTX compared with the MTX group at Week 14. There were statistically significant increases in osteocalcin and PINP levels (Week 4) and significant decreases in DPD (Week 4) and HA (Week 14) levels in combined golimumab + MTX group compared with the MTX group. There were no differences between the treatment groups in lymphocyte subsets ($CD3^+CD4^+$T cells, $CD3^+CD8^+$T cells, $CD3^+CD45RA^+$T cells, $CD3^+CD45RO^+$T cells, $CD14^+$ cells, and $CD19^+$B cells).

Study C0524T11-24wk GO-AFTER was a multicentre, randomised, double-blind, placebo-controlled, 3-arm, parallel study of multiple subcutaneous doses of golimumab in subjects with active RA, previously treated with biologic anti-TNF-α agents. A total of 101 centres received study agent: 60 were in North America and 41 were in Europe/Australia/New Zealand. However, only 86 centres enrolled subjects. The study report presented the data from the 24 week placebo controlled phase, and the extension phase (to Week 268) is intended to be reported separately. Inclusion and exclusion criteria are summarized in Table 7 below:

Table 7. Details of Study C0524T11-24wk GO-AFTER

Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Multicentre, randomised, double-blind, placebo-controlled, 3-arm, parallel study of multiple subcutaneous doses of golimumab in subjects with active RA, previously treated with biologic anti-TNF-α agents	461 subjects were randomised: 155 to placebo, 153 to golimumab 50 mg, and 153 to golimumab 100 mg 367 (79.6%) were female and 94 (20.4%) were male age range 23 to 83 years 102 (65.8%) in the placebo group, 103 (67.8%) in the golimumab 50 mg and 100 (65.8%) in the golimumab 100 mg were taking MTX at baseline	Men or women 18 years of age or older; Diagnosis of RA for at least 3 months prior to screening; Active RA, defined as persistent disease activity with at least 4 swollen and 4 tender joints; Documentation of previous treatment with at least 1 dose of a biologic anti-TNF-α agent (ie, etanercept, adalimumab, or infliximab) at least 12 weeks (infliximab) or 8 weeks (adalimumab or etanercept) prior to the first administration of study agent Identifiable reason (ie, lack of efficacy, intolerance, or "other," which mainly included cost factors) for discontinuing prior anti-TNFα therapy	1. golimumab 50 mg 2. golimumab 100 mg Administered by subcutaneous injection at Weeks 0, 4, 8, 12, 16, and 20 Assigned to treatment group using interactive voice response system Stratified by study centre and baseline MTX use	3. placebo	The primary efficacy outcome measure was the proportion of subjects with an ACR 20 response at Week 14. Secondary efficacy outcome measures included: ACR 50 response at Week 14 DAS28 (using CRP) response at Week 14 ACR 20 response at Week 24 Improvement from baseline in HAQ score at Week 24 ACR 70 and ACR 90 responses at Week 14 ACR 50, ACR 70, and ACR 90 response at Week 24	For the primary efficacy outcome measure, ACR 20, there was superior efficacy for both golimumab groups compared with placebo. There appeared to be greater response in the subgroup treated with MTX but this was not hypothesis tested. For ACR 50 at Week 14 there was also superior efficacy for both golimumab groups. The proportion of DAS 28 (using CRP) responders was greater in the golimumab groups at Week 14. ACR 20 response at Week 24 was greater in the golimumab groups. HAS score at Week 24 improved to a greater extent in the golimumab groups. The proportion of subjects achieving ACR 70 Week 14 was 9.8% in the combined golimumab group compared with 1.9% in the placebo group (p = 0.002)	112 (72.3%) subjects in the placebo group experience one or more AE compared with 256 (68.1%) who were treated with golimumab. The overall AE rates were similar for the three treatment groups as was the overall pattern of AEs. A total of 376 subjects were treated with golimumab and the median (range) of exposure to golimumab was 300 (50 to 600) mg. One subject in the placebo group died from metastatic pancreatic cancer. 11 (7.1%) subjects in the placebo group, 8 (5.3%) in the golimumab 50 mg and 4 (2.6%) in the golimumab 100 mg experienced one or more SAE. 8 (3.9%) subjects in the placebo group, 3 (2.0%) in the golimumab 50 mg and 2 (1.3%) in the golimumab 100 mg discontinued because of an AE. 8 (3.7%) of patients treated with golimumab developed antibodies

The study treatments were golimumab 50 mg, golimumab 100 mg or placebo.

The treatments were administered by subcutaneous injection at Weeks 0, 4, 8, 12, 16, and 20. Assigned to treatment group was performed using interactive voice response system. Subjects were stratified by study centre and baseline MTX use. The study report covered 24 weeks, and subjects had the opportunity of early escape (change of treatment group) in a double blinded fashion from Week 16: placebo to golimumab 50 mg; golimumab 50 mg to golimumab 100 mg. The early escape criteria were: subjects in any group who had < 20% improvement from baseline in both SJC and TJC. At Week 24 the remaining patients in the placebo group were commenced on golimumab 50 mg.

The primary efficacy outcome measure was the proportion of subjects with an ACR 20 response at Week 14. Secondary efficacy outcome measures were:

- ACR 50 response at Week 14
- DAS28 (using CRP) response at Week 14
- ACR 20 response at Week 24
- Improvement from baseline in HAQ score at Week 24
- ACR 70 and ACR 90 responses at Week 14
- ACR 50, ACR 70, and ACR 90 response at Week 24
- ACR 20, ACR 50, ACR 70, and ACR 90 responses over time
- Percent improvement from baseline in SJC, TJC and CRP were summarized at each visit through Week 24
- DAS28 (using CRP) response at Week 24
- DAS28 (using erythrocyte sedimentation rate [ESR]) response at Weeks 14 and 24
- DAS28 remission (using CRP and ESR) at Weeks 14 and 24
- The change from baseline in DAS28 (using CRP and ESR) was summarized at each visit through Week 24.
- ACR-N index of improvement was summarized and compared between treatment groups at Weeks 14 and 24
- Change from baseline in FACIT-F score at Weeks 14 and 24
- Change from baseline in WLQ score at Weeks 14 and 24
- Healthcare utilization, time lost from work, change in employability, and change in productivity
- Change in haemoglobin levels

Hypothesis testing was performed using the Cochran-Mantel-Haenszel test, chi-square test, and ANOVA on the van der Waerden normal scores.

A total of 461 subjects were randomised: 155 to placebo, 153 to golimumab 50 mg, and 153 to golimumab 100 mg. Of the randomised subjects, 367 (79.6%) were female, 94 (20.4%) were male and the age range was 23 to 83 years. From Week 16, 72 (46.5%) subjects in the placebo group transferred to golimumab 50 mg and 41 (27.0%) in the golimumab 50 mg group transferred to golimumab 100 mg. There were 102 (65.8%) subjects in the placebo group, 103 (67.8%) in the golimumab 50 mg and 100 (65.8%) in the golimumab 100 mg taking MTX at baseline. The treatment groups were similar in baseline demographic characteristics, disease duration and disease severity. Prior exposure to anti-TNF-α agents was similar for the three treatment groups. Concomitant DMARD treatment was also similar for the three treatment groups at baseline.

For the primary efficacy outcome measure, ACR 20, there was superior efficacy for both golimumab groups compared with placebo. There appeared to be greater response in the subgroup treated with MTX but this was not hypothesis tested. For ACR 50 at Week 14 there was also superior efficacy for both golimumab groups. The proportion of DAS 28 (using CRP) responders was greater in the golimumab groups at Week 14. ACR 20 response at Week 24 was greater in the golimumab groups. HAS score at Week 24 improved to a greater extent in the golimumab groups. The proportion of subjects achieving ACR 70 Week 14 was 9.8% in the combined golimumab group compared with 1.9% in the placebo group ($p = 0.002$), and at Week 24 was 11.1% in the combined golimumab group and 3.2% in the placebo group ($p = 0.004$). ACR 50 response at Week 24 was 19.3% in the combined golimumab group and 5.2% in the placebo group ($p < 0.001$). There was no significant difference between the treatment groups in ACR 90 response at Week 14 or Week 24. The improvements in ACR 20, ACR 50 and ACR 70 responses occurred in the golimumab groups from Week 4. There were improvements in SJC, TJC and CRP in the golimumab groups from Week 4 but these did not undergo hypothesis testing. There were greater proportions of subjects in both golimumab groups achieving DAS 28 (using CRP) response at Week 24. There were greater proportions of subjects in both golimumab groups achieving DAS 28

(using ESR) response at Week 14 and Week 24. The improvement in DAS scores occurred from Week 4. There was a clinically and statistically significant improvement in FACIT-F scores compared with placebo for both golimumab groups at Week 14 and Week 24. There was a significant improvement in Work Limitations Questionnaire at Week 14 for the combined golimumab group compared with placebo: mean (SD) change from baseline 0.011 (0.0645) for placebo and -0.006 (0.0480) for the combined golimumab group ($p<0.05$).

There were no significant differences between the treatment groups in healthcare utilization, time lost from work for subjects and time lost from work for caregiver. There were improvements from baseline in visual analogue scale for productivity for both golimumab groups compared with placebo. There were no differences between the treatment groups in change in haemoglobin from baseline. There was little difference between golimumab 50 mg and golimumab 100 mg for any of these outcome measures.

In the combined golimumab group there were decreases in ICAM-1, TNF-α, VEGF, MMP-3, and IL-8 during the study. In the combined golimumab group there was a decrease in rheumatoid factor, but not in anti-CCP antibodies.

Additional data provided by the Sponsor as an Addendum

Further data were provided in an addendum reporting efficacy data to Week 52 for Study C0524T05, C0524T06 and C0524T08. ACR 20 response at Week 52 for golimumab 50 mg for subjects who did not change treatment was 76.8%, 82.9% and 78.4% respectively. For golimumab 100 mg, efficacy was also maintained, but there was little difference in comparison with the 50 mg dose groups. Efficacy also appeared to be maintained when measured by ACR 50 and ACR 70. In Study C0524T05, intention to treat analysis also demonstrated maintenance of efficacy through to Week 52. Improvement in DAS, CRP, SJC and TJC were maintained in Study C0524T05 through to Week 52. Improvement in HAQ, DAS, CRP, SJC and TJC were maintained in Study C0524T06 and Study C0524T08 through to Week 52 for both the 50 mg and 100 mg doses.

Evaluator's comments:

Golimumab had superior efficacy to placebo in patients with AS who had not responded adequately to NSAIDs. There was no significant difference in efficacy between golimumab 50 mg and golimumab 100 mg.

Golimumab had superior efficacy to placebo in patients with active psoriatic arthritis. There was no significant difference in efficacy between golimumab 50 mg and golimumab 100 mg.

With regard to RA:

- Study C0524T02 demonstrated that as add-on therapy with MTX, in subjects previously treated with MTX and no previous anti-TNF-α, golimumab 100 mg every 2 weeks was superior to placebo.
- Study C0524T05-24wk GO-BEFORE, demonstrated that Golimumab + MTX superior to MTX alone, with no difference between the 50 mg and 100 mg doses, in MTX naïve subjects with no previous anti-TNF-α treatment. Golimumab was non-inferior to MTX, using clinically relevant criteria for non-inferiority, but this was not the primary analysis of the study.
- Study C0524T-06-24wk demonstrated that in subjects with previous MTX treatment, golimumab + MTX was superior to MTX alone, with no significant difference between golimumab 50 mg and 100mg. Golimumab alone was not superior to MTX and non-inferiority was not tested.
- Study C0524T11-24wk GO-AFTER demonstrated superior efficacy for both 50 mg and 100 mg golimumab groups compared with placebo in patients with previous anti-TNF-α treatment. There appeared to be greater response in the subgroup treated with MTX but this was not hypothesis tested.

Safety

Safety data from efficacy studies

For ***Study C0524T09-24wk***, summarised in Table 2, AEs occurred to a similar extent in all treatment groups, but upper respiratory tract infection, elevated ALT, elevated AST, diarrhoea and headache occurred more frequently with golimumab. AEs were reported in 59 (76.6%) of subjects treated only with placebo and 255 (79.9%) of subjects who received golimumab. SAEs were reported in four (5.2%) subjects in the placebo group, five (3.6%) in the golimumab 50 mg and seven (5.0%) in the golimumab 100 mg. There were no deaths reported during the study. No cases of TB were reported. Infections requiring oral or parenteral antimicrobial treatment through Week 24 occurred in 14.3% of subjects in the placebo group and 23.7% in the combined golimumab group (18.8% in the golimumab 50 mg and 27.9% in the 100 mg group). One (1.3%) subject in the placebo group and seven (2.5%) in the golimumab discontinued because of AEs. Eleven (3.5%) of patients treated with golimumab developed antibodies. One (1.3%) subjects in the placebo group and two (0.7%) in the golimumab 100 mg were reported as having one or more serious infections. One subject in the placebo group and one in the golimumab 100 mg were reported as developing malignancies (in both cases basal cell carcinomas). Seven (2.2%) subjects in the golimumab group had marked elevations of ALT and three had marked elevations of AST.

In ***Study C0524T08*** summarised in Table 3, the overall rate of AEs was higher in the golimumab groups at 64.7%, than in the placebo group at 59.3%. Nasopharyngitis and upper respiratory tract infection were more common in patients treated with golimumab. No deaths were reported during the 24 week study period. SAEs were reported in six (5.3%) subjects in the placebo group, three (2.1%) in the golimumab 50 mg, and two (1.4%) in the golimumab 100 mg. Infections were reported in 23 (20.4%) subjects in the placebo group, 36 (24.7%) in the golimumab 50 mg and 39 (26.7%) in the golimumab 100 mg. SAEs due to infection were reported more commonly in the placebo group. Seventeen (15.0%) subjects who received only placebo required antimicrobial treatment compared with 58 (15.7%) subjects who received any golimumab. No cases of latent or active TB were diagnosed during the study. Golimumab did not appear to affect the response to pneumococcal vaccination. Malignancies were reported in three subjects in the golimumab 100 mg group: basal cell carcinoma (2) and prostate cancer (1). There were no significant differences between the groups in haematology or clinical chemistry parameters. Elevations in ALT occurred in 4 (3.6%) subjects in the placebo group and 3 (0.9%) in the golimumab groups. Elevations in AST occurred in 3 (2.7%) subjects in the placebo group and 2 (0.6%) in the golimumab groups.

For ***Study C0524T02*** summarized in Table 4, up to crossover (placebo group switching to infliximab) at Week 20, the frequency of subjects with one or more AEs was similar for placebo: 29 (85%) subjects; as for golimumab: 118 (86.1%) subjects. Up to Week 52, the proportion of subjects with at least on AE appears to be higher for the golimumab treated subjects but the duration of treatment was longer for this group. The proportion of subjects with at least one AE was 29 (85.3%) subjects for placebo, 16 (64.0%) for infliximab and 130 (94.9%) for golimumab. One subject died 4 months after last administration of golimumab. There were no deaths reported as occurring during the study.

Up to crossover at Week 20, SAEs were reported in two (5.9%) subjects in the placebo group, four (10.8%) in the golimumab 50 mg, 4 weekly; three (9.4%) in the golimumab 50 mg 2 weekly; two (6.1%) in the golimumab 4 weekly; and three (8.6%) in the golimumab 100 mg, 2 weekly. Up to Week 52, SAEs were reported in two (5.9%) subjects in the placebo group, three (12.0%) in the infliximab, seven (18.9%) in the golimumab 50 mg, 4 weekly; five (15.6%) in the golimumab 50 mg 2 weekly; five (15.2%) in the golimumab 4 weekly; and five (14.3%) in the golimumab 100 mg, 2 weekly. The rates of treatment emergent infections, up to Week 20, were similar for the five treatment groups. Prior to Week 20, three (8.6%) subjects in the placebo group and nine (6.6%) in

the golimumab discontinued because of AEs. To Week 52, six (17.1%) subjects in the placebo/infliximab group and 16 (9.3%) in the golimumab discontinued because of AEs. Nine (8.2%) of subjects developed antibodies to golimumab through to Week 52, 19 (17.3%) developed antibodies through to Week 68.

Malignancies were reported in four golimumab treated subjects: two with basal cell carcinoma, one with squamous cell and basal cell carcinomas and one with lung adenocarcinoma. Up to crossover at Week 20 markedly abnormal elevations in post-baseline ALT level were observed in 4 (2.9%) subjects in the combined golimumab plus MTX group and one (2.9%) in the placebo plus MTX group. Through to Week 52, elevation in post-baseline ALT level occurred in 11 (8.0%) subjects in the golimumab groups and one (2.9%) in the placebo group. Newly positive ANA tests occurred in 27 (21.3%) subjects in the golimumab treatment groups and five (17.9%) in the placebo group.

For ***Study C0524T05-24wk GO-BEFORE*** summarized in Table 5, the percentage of subjects reporting at least one AE was lower in the golimumab 100 mg alone group than in the other three treatment groups. The number (%) of subjects with at least one AE was 116 (72.5%) in the MTX group, 107 (68.2%) in the golimumab 100 mg, 129 (81.6%) in the golimumab 50 mg + MTX and 121 (76.1%) in the golimumab 100 mg + MTX. There were fewer subjects with nausea and elevated ALT in the golimumab alone group. Two subjects died during the 24 week study period: one subject in the golimumab 50 mg + MTX group from hypoglycaemic coma after a suicide act involving insulin injection; one subject in the golimumab 100 mg + MTX group from cardiorespiratory arrest after a gluteal abscess evacuation surgery. The number (%) of subjects with at least one SAE was eleven (6.9%) in the MTX group, five (3.2%) in the golimumab 100 mg, ten (6.3%) in the golimumab 50 mg + MTX and ten (6.3%) in the golimumab 100 mg + MTX. Discontinuations because of AEs occurred in one (0.6%) subject in the MTX group, one (0.6%) in the golimumab 100 mg, five (3.1%) in the golimumab 50 mg + MTX and six (3.8%) in the golimumab 100mg + MTX.

The number (%) of subjects with at least one infection was similar for each treatment group: 52 (32.5%) in the MTX group, 55 (35.0%) in the golimumab 100 mg, 54 (34.2%) in the golimumab 50 mg + MTX and 50 (31.4%) in the golimumab 100 mg + MTX. The proportion of subjects with serious infections was highest in the golimumab 100 mg + MTX group. One subject in the golimumab 50 mg + MTX group was diagnosed with TB of the spine after the start of study agent.

Four subjects were reported to have malignancies during the study: two subjects in the MTX alone group (one with breast cancer; one with squamous cell skin carcinoma); one subject in the golimumab 50 mg + MTX group (breast cancer in situ); and one subject in the golimumab 100 mg + MTX group (Hodgkin's lymphoma). Three (1.9%) subjects in the golimumab 100 mg + MTX group had a fall in neutrophil count of >33%. The pattern of subjects with ALT elevation suggests MTX is more likely associated than golimumab. However the pattern of AST elevation suggests that golimumab was more likely associated than MTX.

In ***Study C0524T-06-24wk*** summarised in Table 6, AEs were reported in 90 (67.7%) subjects who were treated with MTX alone, 93 (69.9%) treated with golimumab alone and 174 (68.2%) treated with golimumab + MTX. Upper respiratory tract infections were the most common AE in all the treatment groups. The median (range) dose of golimumab was 300 (200 to 600) mg. SAEs occurred in three (2.3%) subjects in the MTX group, five (3.8%) in the golimumab, five (5.6%) in the golimumab 50 mg + MTX and eight (9.0%) in the golimumab 100 mg + MTX.

To Week 16, one or more infections were reported in 32 (24.1%) subjects in the MTX group, 40 (30.1%) in the golimumab, 25 (28.1%) in the golimumab 50 mg + MTX and 25 (28.1%) in the golimumab 100 mg + MTX. One or more serious infections occurred in one (0.8%) subjects in the MTX group, three (2.3%) in the golimumab and eight (3.1%) in the golimumab + MTX. One patient in the golimumab alone group died from sepsis. Six (4.5%) subjects in the MTX group discontinued subcutaneous study agent because of an AE, six (4.5%) for golimumab, two (2.2%) for

golimumab 50 mg + MTX and five (5.6%) for golimumab 100 mg + MTX. Three (1.5%) golimumab treated subjects developed antibodies.

Four subjects were reported as developing malignancies: one in the MTX group: basal cell carcinoma; two in the golimumab: squamous cell skin carcinoma and basal cell carcinoma; and one in the golimumab 100 mg + MTX group: breast cancer. In patients that did not receive TB prophylaxis, there were fewer patients with elevations of ALT or AST than in the groups treated with MTX.

In ***Study C0524T11-24wk GO-AFTER*** summarised in Table 7, 112 (72.3%) subjects in the placebo group experience one or more AE compared with 256 (68.1%) who were treated with golimumab. The overall AE rates were similar for the three treatment groups as was the overall pattern of AEs. A total of 376 subjects were treated with golimumab and the median (range) of exposure to golimumab was 300 (50 to 600) mg. One subject in the placebo group died from metastatic pancreatic cancer. Eleven (7.1%) subjects in the placebo group, eight (5.3%) in the golimumab 50 mg and four (2.6%) in the golimumab 100 mg experienced one or more SAE. One or more infections was reported in 43 (27.7%) subjects in the placebo group, 41 (27.0%) in the golimumab 50 mg and 38 (25.0%) in the golimumab 100 mg. The rate of serious infections was not increased in the golimumab groups. Three malignancies were reported: one in the placebo group: metastatic pancreatic cancer; on in the golimumab 50 mg group: squamous cell skin carcinoma; and one in the golimumab 100 mg group: lymphoma. Of the patients not receiving treatment for TB, a greater proportion had elevations in ALT in the golimumab groups. A slightly higher proportion in the golimumab groups had elevations in AST.

Safety data from pharmacodynamic studies

In ***Study C0466T01***, AEs were reported in four (40%) subjects in the placebo group, three (100%) in the golimumab 0.1 mg.kg, one (33.3%) in the 0.3 mg/kg, four (80%) in the 1 mg/kg, four (80%) in the 3 mg/kg, five (100%) in the 5 mg/kg and five (100%) in the 10 mg/kg. In the golimumab treated subjects the most common AE across all groups was headache, occurring in six of 26 subjects. Five of the six subjects experiencing headache were in the highest-dose group. Eight subjects (one who received placebo and seven who received golimumab) experienced one or more infections: cystitis, respiratory tract infection, vaginitis, urinary tract infection, pneumonia, thrush, toe infection, and infection at an old surgical site. There was one SAE: femoral to femoral bypass with postoperative wound infection. Four subjects in the golimumab groups had elevations in ALT and two had increases in CK. Three subjects developed antibodies to golimumab.

In ***Study C0466T02***, during Stage I (single dose) four (80%) subjects in the 0.3 mg/kg dose group, three (60%) in the 0.6 mg/kg, two (40%) in the 1.0 mg/kg, one (20%) in the 3.0 mg/kg and six (66.7%) in the placebo experienced one or more AEs. In the golimumab groups, the commonest AEs were: abdominal pain, coughing, headache, injection site haematoma, injection site pain, pharyngitis, rash and vomiting (each of which was reported in two (10%) subjects). During Stage II (multiple dose), AEs were experienced by four (66.7%) subjects in the 0.3mg/kg group, seven (87.5%) in the 1.0 mg/kg group and seven (77.8%) in the placebo. In the golimumab groups, the commonest AEs were: viral infection, injection site pruritis, headache and dizziness (each of which was reported in two (14.3%) subjects). There were no deaths. One malignancy was reported during the study, in the placebo group.

Safety data from bioequivalence studies

In ***Study C0524T24***, 67 (42.9%) subjects reported one or more AE; 39 (49.4%) in the needle and syringe group, 28 (36.4%) in the autoinjector group. The commonest AEs were: pharyngolaryngeal pain 17 (10.9%) subjects, headache twelve (7.7%), nasopharyngitis eight (5.1%), cough five (3.2%), nasal congestion four (2.6%), arthralgia three (1.9%), contusion three (1.9%), joint sprain three (1.9%), myalgia three (1.9%) and vomiting three (1.9%). There was one SAE: myocarditis one

month after study completion. The investigator considered the myocarditis was unlikely to be related to the study treatment. There were no deaths. Golimumab antibodies occurred in one (1.3%) subject in each treatment group.

Safety data from pharmacokinetic studies

In ***Study C0524T13***, there were 16 (53.3%) subjects that had at least one AE. The most common AEs were: headache 5 (16.7%) subjects, and dyspepsia 2 (6.7%). There were no SAEs or deaths. One (3.3%) subject had an increase in ALT. None of the subjects were classified as positive for golimumab antibodies.

In ***Study C0524T23***, there 23 (45.1%) of 51 subjects reported AEs. For the 100 mg dose, eight (66.7%) Japanese subjects and six (46.2%) Caucasian subjects reported AEs. For the 50 mg dose, four (33.3%) Japanese subjects and five (35.7%) Caucasian subjects reported AEs. The commonest AEs were: headache four (7.8%) subjects, pharyngolaryngeal pain four (7.8%), upper respiratory tract infection three (5.9%), upper abdominal pain three (5.9%), vomiting two (3.9%), and arthropod bite two (3.9%). There were no SAEs, deaths or withdrawals due to AEs reported during the study. None of the study subjects were positive for antibodies to golimumab. There were no clinically significant changes in laboratory tests.

In ***Study C0524T03***, one or more AEs were reported in 70 (89.7%) subjects in the placebo group, 64 (85.3%) in the golimumab 50 mg, 74 (94.9%) in the golimumab 100 mg, and 73 (93.6%) in the golimumab 200 mg. The commonest infective AEs in the golimumab treated patients were: sinusitis 19 (8.2%) subjects, nasopharyngitis seven (7.4%), URTI 17 (7.4%), bronchitis eleven (4.8%), pneumonia eleven (4.8%) and rhinitis eleven (4.8%). One subject in the golimumab 200 mg group died from septic shock, which was considered by the investigator to be possibly related to the study treatment. SAEs were reported in six (7.7%) subjects in the placebo group, eleven (14.7%) in the golimumab 50 mg, 14 (17.9%) in the golimumab 100 mg and 13 (16.7%) in the golimumab 200 mg. Infective SAEs were more frequent with golimumab: no (0.0%) subjects in the placebo group, three (4.0%) in the golimumab 50 mg, five (6.4%) in the golimumab 100 mg and five (6.4%) in the golimumab 200 mg. The exposure to golimumab ranged from 300 to 2900 mg. Ten (5%) subjects exposed to golimumab developed antibodies. The commonest infective AEs in the golimumab treated patients were: sinusitis 19 (8.2%) subjects, nasopharyngitis 17 (7.4%), URTI 17 (7.4%), bronchitis eleven (4.8%), pneumonia eleven (4.8%) and rhinitis eleven (4.8%). Discontinuation because of AEs occurred in four (5.1%) subjects in the placebo group, 13 (17.3%) in the golimumab 50 mg, 15 (19.2%) in the golimumab 100 mg and twelve (15.4%) in the golimumab 200 mg. One (1.5%) subject in the placebo group and 26 (13.6%) in the combined golimumab group developed antinuclear antibodies. One subject in the golimumab 100 mg group developed anti-double stranded DNA antibodies.

Additional safety data

An Integrated Summary of Safety was provided as a report. No additional studies were described in the report. In total, for the indications applied for in the submission, there were 2154 subjects treated with golimumab, with 1877 subjects treated for at least 6 months (24 weeks) and 926 subjects treated for at least 1 year (52 weeks). In the pooled Phase 3 RA studies 1180 subjects treated with golimumab for at least 6 months (24 weeks) and 512 subjects treated with golimumab for at least 1 year (52 weeks). In the PsA study: 372 subjects treated for at least 6 months (24 weeks) and 254 subjects treated for at least 1 year (52 weeks). In the AS study: 325 subjects treated for at least 6 months (24 weeks) and 160 subjects treated for at least 1 year (52 weeks). The pattern of AEs presented in the pooled analysis was similar to that emerging from the individual studies. There were slightly more patients in the golimumab treated groups that had elevations in ALT or AST reported as AEs. Uveitis has been attributed to other TNF-α inhibitors, but the rate was not

increased by golimumab in the pivotal studies: 1 (0.2%) subjects in the placebo groups and 3 (0.2%) in the golimumab.

A report titled "Supportive Analysis for Monthly Administration of Golimumab" was also provided. The report did not include any additional data. The report contained summary tables of the duration between administrations of golimumab and were descriptive rather than analytical.

A report titled "Evaluation of Safety and Antibodies to Golimumab Following Administration With Liquid in Vial or Prefilled Syringe" was also provided. The report did not include any additional data. The rates of injection site AEs and immunogenicity data were similar for the two administration methods.

Study C0524T01 was a double-blind, placebo-controlled, parallel group, multicentre study of golimumab at three fixed dose levels given at 2 week intervals for 10 weeks (6 total doses) for safety, pharmacokinetics, immunogenicity, and clinical response, and followed up for 16 weeks after the last dose of study agent (through Week 26) in subjects with intermediate uveitis, posterior uveitis, or panuveitis. The study included males or females ≥18 years of age with a diagnosis of intermediate uveitis, posterior uveitis, or panuveitis of a noninfectious etiology. The study treatments were: golimumab 50 mg, golimumab 100 mg, golimumab 200 mg, and placebo. The safety outcome measures were: AEs (including injection site reactions and infections); hematology and clinical chemistry values; vital signs (blood pressure, heart rate, respiratory rate, body temperature); development of ANA, anti-dsDNA antibodies, and antibodies to golimumab. A total of 26 subjects were enrolled: seven received golimumab 50 mg, six received golimumab 100 mg, six received golimumab 200 mg, and seven received placebo. Twenty two (84.6%) subjects were female, four (15.4%) were male and the age range was 19 to 79 years. The efficacy data were not evaluable because of the different indication used in the study. Seven (100.0%) subjects in the placebo group, seven (100.0%) in the golimumab 50 mg, five (83.3%) in the golimumab 100 mg and five (83.3%) in the golimumab 200 mg experienced one or more AEs. The commonest AEs in the golimumab treated patients were: URTI in ten (52.6%) subjects, pain nine (47.4%), headache eight (42.1%), purpura eight (42.1%) and nausea seven (36.8%). Four subjects in the placebo group, one in the golimumab 50 mg and one in the golimumab 100 mg reported one or more SAE. No subjects developed antibodies to golimumab. No deaths were reported during the study.

Safety data relating to the autoinjector device

Study C0999D01 was a phase I, controlled, randomised, cross-over, safety and tolerability study of the autoinjector device in healthy volunteers. No active investigational agent was administered. Subjects were screened up to 4 weeks prior to their first injection, and were randomised to receive 1 mL of placebo administered SC twice, once using the investigational auto-injector device and once using a pre-filled syringe. Injections were made to matching sites on contralateral sides of the body, and were spaced approximately 60 minutes apart. Placebo administered subcutaneously by autoinjector compared with needle and syringe to a total of 60 male and female adult subjects, 18 years or older, in generally good health. Safety assessments included adverse events (AEs), including device-related AEs and injection site AEs; injection site pain (as measured using the Brief Pain Inventory-Short Form [BPI-SF] questionnaire); clinical examination of injection sites for induration, erythema, and SC emphysema; and vital signs. Other assessments included overall subject preference (for the auto-injector or pre-filled syringe).

Seven (11.7%) subjects had at least one treatment-emergent AE. Five (8.3%) subjects reported a total of six treatment emergent injection site reactions; three with the auto-injector: included mild injection site haemorrhage in the upper thigh (one subject), mild injection site bruising in the upper arm (one subject), and moderate injection site pain in the upper arm (one subject); and three with the pre-filled syringe: mild injection site haemorrhage in the upper thigh (one subject), moderate injection site irritation in the upper arm (one subject), and moderate injection site pain in the upper arm (one subject). Mean (SD) peak and time-averaged pain scores were lower with the auto-

injector: 1.1 (1.40) and 0.02 (0.074) respectively, than with the pre-filled syringe 1.3 (1.60) and 0.03 (0.100) respectively. Mean (SD) erythema at the injection site 0.5 hours after injection was 0.7 (3.82) mm for the auto-injector compared with 2.3 (7.56) mm for pre-filled syringe. Mean (SD) induration at the injection site 0.5 hours after injection was 0.5 (2.41) mm for the auto-injector compared with 3.2±8.54 mm for the pre-filled syringe. Overall 43 (71.7%) of 60 subjects preferred the auto-injector over the pre-filled syringe, 15 (25.0%) preferred needle and syringe; and preference was unknown for two (3.3%) subjects. There were no deaths, other serious adverse events (SAEs), or withdrawals due to AEs during this study. No needlestick injures were reported.

Additional safety data provided as an Addendum

The sponsor provided some additional safety data for studies performed up to 52 weeks duration. Rates of some AEs were provided in the form of events per 100 patient years. The incidence per 100 patient years (95% CI) of death was 0.36 (0.18 to 0.62) compared with 0.22 (0.01 to 1.25) for placebo, for serious infections for golimumab was 4.44 (3.71 to 5.26) compared with 5.73 (3.45 to 8.95) for placebo; and for sepsis was 0.54 (0.32 to 0.85) compared with 0.22 (0.01 to 1.25) for placebo. The rate of cellulitis was increased compared 1.84 (1.41 to 2.36) with placebo 1.12 (0.36 to 2.62). The rate of pneumonia was higher in the placebo group. The rate of tuberculosis was 0.24 (0.10 to 0.47) in the golimumab group, and there were no cases reported in the placebo group. The standardised incidence rate for malignancies was increased in the golimumab group: 1.29 (0.84 to 1.91), but this was not statistically significant.

Evaluator's comments:

In subjects treated with golimumab there was an increased rate of upper respiratory infections, an increased rate of serious infections and more infections requiring antibiotic treatment. There were two deaths from sepsis and one from post-operative sepsis. There was one report of myocarditis but no other indication of an excess in cardiac inflammatory conditions. The rate of uveitis was not increased in the golimumab treated groups.

There was no apparent increase in the rate of malignancy. In some studies there was an increase in the rate of subjects with elevation in ALT and AST, but there appeared to be a stronger relationship with MTX than with golimumab. This will need to be further explored in post-marketing studies.

Reactivation of tuberculosis was a rare AE but this may reflect the exclusion studies in the clinical trials. In clinical practice this may prove to be a more frequent AE.

Overall, there were 2154 subjects treated with golimumab, with 1877 subjects treated for at least 6 months (24 weeks) and 926 subjects treated for at least 1 year (52 weeks). Hence there were adequate numbers of patients and duration of treatment for evaluation of safety.

Clinical Summary and Conclusions

The data presented in the submission represent the clinical development program for a new biological entity in the group of drugs that inhibit the action of TNF-α. The mode of action of the drug is not novel. The clinical development program was conducted in 3195 subjects, 2357 of whom were exposed to golimumab. The doses investigated in the Phase III studies were golimumab 50 mg and golimumab 100 mg, and the duration of these studies was from 26 to 52 weeks. Some of the clinical studies are ongoing and further safety data should become available in the near future. Some of the pivotal studies have follow-on open label phases intended to last up to five years. These studies are intended to contribute data to pharmacovigilance studies. Overall, there were 2154 subjects treated with golimumab, with 1877 subjects treated for at least 6 months (24 weeks) and 926 subjects treated for at least 1 year (52 weeks). Hence there were adequate numbers of patients and duration of treatment for evaluation of safety.

The preliminary dose finding studies are discussed under the heading "pharmacodynamics". These studies demonstrate that there has been extensive consideration of the dose used in the efficacy studies. The pharmacodynamic studies examined the effects of golimumab upon inflammatory markers, and the effects of golimumab at different doses upon efficacy measures for RA. These studies also appear to have been used to refine the outcome measures. The *in vitro* studies were useful in examining the nature of anti-golimumab antibodies. These antibodies were neutralizing and directed against the Fab portion of golimumab.

The pharmacokinetic studies were used to study the pharmacokinetics of golimumab in both healthy volunteers and in the target population. The use of population pharmacokinetic studies to investigate the influence of covariates upon golimumab pharmacokinetics was especially useful. Although the pharmacokinetics of golimumab are for the most part linear, there was greater exposure (as measured by AUC) with increasing dose. The pharmacokinetic parameters of golimumab were similar for Japanese and Caucasian subjects. The pharmacokinetic parameters in subjects with severe asthma were similar to healthy volunteers. The pharmacokinetic parameters were not influenced by hepatic or renal disease. Clearance and volume of distribution were primarily determined by body weight. Clearance decreased with increasing CRP. Clearance of golimumab was increased in the presence of anti-golimumab antibodies by 10% to 36%. Clearance of golimumab was increased in smokers by 13%. Concomitant use of methotrexate, sulfasalazine or oral corticosteroids did not significantly influence the population PK parameters. Clearance of golimumab was decreased by concomitant MTX treatment by 17%.

The efficacy studies were performed in highly selected populations, and the choice of comparator group was for the most part placebo rather than active. This may result in restricted indications. In subjects with AS, golimumab had superior efficacy to placebo in patients who had not responded adequately to NSAIDs. Golimumab had superior efficacy to placebo in patients with active psoriatic arthritis.

With regard to subjects with RA, Study C0524T02 demonstrated that as add-on therapy with MTX, in subjects previously treated with MTX and no previous anti-TNF-α, golimumab 100 mg every 2 weeks was superior to placebo. Study C0524T05-24wk GO-BEFORE, demonstrated that Golimumab + MTX was superior to MTX alone, in MTX naïve subjects with no previous anti-TNF-α treatment. Golimumab was non-inferior to MTX, using clinically relevant criteria for non-inferiority, but this was not the primary analysis of the study and therefore carries less weight. Study C0524T-06-24wk demonstrated that in subjects with previous MTX treatment, golimumab + MTX was superior to MTX alone. Golimumab alone was not superior to MTX and non-inferiority was not tested. Study C0524T11-24wk GO-AFTER demonstrated superior efficacy for both 50 mg and 100 mg golimumab groups compared with placebo in patients with previous anti-TNF-α treatment. There appeared to be greater response in the subgroup treated with MTX but this was not hypothesis tested.

In subjects with AS, psoriatic arthritis and RA, there was no significant difference in efficacy between golimumab 50 mg and golimumab 100 mg.

Safety across individual studies showed golimumab was associated with more frequent reports of URTI, infections, serious infections, fatigue, ALT/AST elevated, diarrhoea, nausea, headache, infections requiring antibiotics, nasopharyngitis, newly positive ANA tests and injection site reactions. Golimumab did not appear to affect the response to pneumococcal vaccination. A small study in patients with uveitis using doses up to 200mg of golimumab showed the commonest adverse events were URTI, pain, headache, purpura and nausea. A safety study using the autoinjector showed 72% preferred it to the needle/syringe (25%).

For patients on 52 weeks of treatment, the following incidences per 100 patient years are noted on golimumab compared to placebo: death (0.36 vs. 0.22), serious infections (4.44 vs. 5.73), sepsis (0.54 vs. 0.22), cellulitis (1.84 vs. 1.12), pneumonia (2.44 vs. 2.92) and tuberculosis (0.24 vs. 0.0).

The standardised incidence rate for malignancies was increased on golimumab at 1.29 (0.84 to 1.91) compared with placebo at 0.74 (0.09 to 2.69). Cases of lymphoma were noted in golimumab patients. There were two deaths from sepsis and one related to post-operative sepsis. There was one report of myocarditis. The elevation in liver enzymes seen was greater on golimumab than placebo but also seen with methotrexate. Reactivation of tuberculosis was a rare adverse event.

The bioequivalence study demonstrated that administration of golimumab using the autoinjector device was bioequivalent to injection by needle and syringe. A safety study performed with the autoinjector device demonstrated similar safety and tolerability compared to needle and syringe.

Deficiencies in the Submission

There were no comparator controlled studies for AS and psoriatic arthritis. The only active comparator used in the studies conducted in subjects with RA used MTX. Hence there are few data comparing golimumab with other drugs, either in the same class (TNF-α inhibitors) or DMARDs and NSAIDs. It will be difficult for clinicians to determine the place of golimumab in the treatment algorithm. Clinicians will need to consider which TNF-α should be preferred, or even used as first line agents, and which combinations of agents should be used in clinical practice. The current data do not enable these decisions to be made.

The duration of the studies presented in the submission was 12 months at the longest. Further data were provided in an addendum to Module 5 reporting efficacy data to Week 52 for Study C0524T05, C0524T06 and C0524T08 indicating continuing efficacy and safety to Week 52. There were no data demonstrating the long term safety and efficacy of golimumab beyond 52 weeks.

The sponsor was asked to address the following issues in their pre-ADEC response:

- The implementation of a Risk Management Plan for Simponi for these indications in Australia, which will form a condition of registration. Such a plan should include monitoring for infections, malignancies and hepatic adverse events.
- The 90% confidence intervals for bioavailability from subcutaneous injection into the abdomen, upper arm and thigh and what are the clinical implications from any bioinequivalence.
- A summary table of elevations in ALT and AST for golimumab 50mg, golimumab combined, methotrexate and placebo using >3xULN, >5xULN and >8xULN and also include all clinical hepatic reports.
- A table of all malignancies during the entire clinical trial programme as reported for golimumab, placebo and methotrexate, including type of malignancy, frequency and expected rate according to the SEER database.
- A discussion on cardiac failure and autoimmune disorders reported with golimumab.

These were all provided.

Recommendations of the Clinical Evaluator

The clinical evaluator recommended that golimumab (Simponi) should be rejected for all three of the indications sought by the sponsor.

The indication for AS is not consistent with the inclusion criteria used in the study, which was "patients who had not responded adequately to NSAIDs". The statement "*Simponi has also been shown to improve physical function and health related quality of life"* is not an indication, but rather a statement of efficacy, and should be removed from the indications. The functional and health related quality of life measures were secondary rather than primary outcome measures in the pivotal studies.

The studies conducted in RA did not evaluate golimumab as a first choice of anti-TNFα agent. There are no data demonstrating comparative efficacy with other anti-TNF-α drugs for any of RA, AS or psoriatic arthritis. Instead, the data support the use of golimumab as a second line anti-TNF-α agent in RA. In addition, there are insufficient data to support golimumab as an alternative to MTX, rather the data support golimumab in addition to MTX where the patient has not responded adequately to MTX.

There are insufficient data to support golimumab as a first-line TNF-α inhibitor in patients with AS or psoriatic arthritis, because of the lack of comparative efficacy data with other TNF-α inhibitors. It is not known whether golimumab might have inferior efficacy and/or safety to other TNF-α inhibitors for all three indications.

Hence, the clinical evaluator is of the opinion that there is insufficient evidence to support the sponsor's indications as presently worded:

Rheumatoid arthritis (RA)

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

- *the treatment of: active rheumatoid arthritis in adult patients when the response to Disease Modifying Anti-Rheumatic Drug (DMARD) therapy has been inadequate*
- *the treatment of active rheumatoid arthritis in adult patients not previously treated with MTX*

Simponi has also been shown to improve physical function and health related quality of life. Simponi can also be used in patients previously treated with one or more TNF inhibitor(s).

Psoriatic arthritis (PsA)

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

The treatment of active psoriatic arthritis in adult patients when the response to previous DMARD has been inadequate. Simponi has also been shown to improve physical function and health related quality of life.

Ankylosing spondylitis (AS)

Simponi is indicated for:

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

However, golimumab (Simponi) should instead be approved for the following alternative indications:

Rheumatoid arthritis (RA)

Simponi, in combination with methotrexate (MTX) is indicated for the treatment of: active rheumatoid arthritis in adult patients when the response to MTX, Disease Modifying Anti-Rheumatic Drug (DMARD) and/or TNF inhibitor therapy, singly or in combination, has been inadequate.

Psoriatic arthritis (PsA)

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

The treatment of active psoriatic arthritis in adult patients when the response to previous DMARD and TNF inhibitor therapy, singly or in combination, has been inadequate.

Ankylosing spondylitis (AS)

Simponi is indicated for:

The treatment of active ankylosing spondylitis in adult patients when the response to NSAIDs and TNF inhibitor therapy, singly or in combination, has been inadequate.

These alternative indications are more consistent with the design of the pivotal studies, the duration of follow-up evaluable for efficacy, and the results of the pivotal studies.

A further recommendation is that a pharmacovigilance plan be developed to monitor the long-term safety of golimumab, with particular attention to infections, malignancies and hepatitis adverse reactions.

V. Pharmacovigilance Findings

There were no pharmacovigilance studies or plans submitted.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the Delegate's overview and recommendation.

Quality

Approval is recommended from a biochemistry, quality control and bioavailability aspect. Simponi is supplied as a sterile solution in a single use prefilled syringe or autoinjector pen. One GMP clearance remains outstanding but otherwise all other Module 3 matters have been resolved. Two bioavailability studies were conducted using a parallel design. The first investigated absolute bioavailability from administration of golimumab into the upper arm, abdomen and thigh and noted that bioavailability from subcutaneous injection was about 51% with similar bioavailability from the three injection sites (47-54%). However bioequivalence using standard 90% confidence intervals were not calculated and if they were then it is likely they would fall outside the 80-125% interval. The second study investigated bioavailability of the auto-injector compared with a needle and syringe and showed bioequivalence in terms of AUC, but the Cmax had a 90% confidence interval of 96-127%, which just exceeded the usual upper limit of 125%. The sponsor re-calculated the results with the exclusion of 8 subjects who had "wet injections", i.e. notable amount of injection fluid that leaked from the injection site, and now the AUC and Cmax were both within the standard 80-125% confidence interval.

Non-Clinical

There were no non-clinical findings that precluded approval of the submission. Repeat dose toxicity studies in monkeys using high doses of golimumab showed few treatment effects (slight increases in T-cell subsets and B-cells) and an intravenous study in mice showed no toxicity. Golimumab was generally well tolerated in the toxicity studies, which is consistent with its high specificity and lack of cross-reactivity with tissue components. Minor binding to skin epithelium was seen. Golimumab was immunogenic in monkeys but this did not result in untoward effects. No genotoxicity or carcinogenicity studies were conducted, as expected for this type of product. Reproductive toxicity studies showed slightly reduced fertility at high doses in mice (40mg/kg/week) but not at lower doses. Golimumab crosses the placenta and was measured in low concentrations in maternal milk. Minor injection site reactions were seen, including mild vasculitis with 2x weekly injections. No studies were done in combination with methotrexate.

Clinical

The clinical evaluator has recommended approval. Issues noted by the evaluator included:

Efficacy studies were performed in highly selected populations.

Efficacy studies in psoriatic arthritis and ankylosing spondylitis only used placebo as a comparator.

There was no dose response between 50mg and 100mg dosing.

There are no data comparing golimumab with other TNF inhibitors. There was one study in RA patients in which patients discontinued previous therapy with one or more TNF inhibitors for a variety of reasons, including lack of efficacy.
The data support use of golimumab as a second line agent.

Risk-Benefit Analysis

Bioavailability and PSC concerns: The two bioavailability studies conducted were both parallel design, rather than a crossover design as would normally be expected. The sponsor justified this by noting the long half life (12 days), potential immunogenicity, intention to minimise exposure to healthy volunteers and the ability to achieve statistical power. This was considered unacceptable by PSC but considered acceptable by the pharmaceutical chemistry evaluator. Given a cross-over design would have required a washout period of 120 days plus a further 70 days for blood sampling, then the total study duration would have been 7 months which could have led to considerable loss to follow up of subjects. The immunogenicity rate was only 5% and the sponsor has agreed with PSC that this was low. EU guidelines on this matter note that a parallel design is acceptable for drugs with a very long half life. Overall, the sponsor's justification appears acceptable. Bioavailability was similar from the three injection sites of 47% abdomen, 53% upper arm and 54% thigh, however no 90% confidence intervals were calculated. The sponsor should address this issue. Although bioequivalence between autoinjector and needle/syringe was seen for AUC, a higher Cmax from the autoinjector (90% CI 96, 127%) is unlikely to be clinically significant, given it is just outside the usual upper limit and that doses of 100mg demonstrated similar clinical safety to the proposed 50mg injection. The PSC noted some issues from the population pharmacokinetic modelling that implied non-linearity of golimumab, however the sponsor and clinical evaluator have concluded overall, based on the clinical data, that golimumab mostly appears to exhibit linear pharmacokinetics.

NGNA and gal-alpha-gal glycans: Golimumab contains significant levels of glycans not commonly found in humans. Glycans with these structures can induce an immune response and due to the exposure to these structures in food, animals and microbes then most humans are claimed to already possess pre-existing antibodies to them. The clinical experience from over 2000 patients did not suggest an immunogenic response based on no anaphylaxis reported, low antibody response of 5% to golimumab, low and mostly mild injection site reactions and neutralising antibodies that did develop were directed against the Fab region and not the Fc region where the glycans reside.

Prior TNF inhibitor use: The clinical evaluator has commented on restricting the indications to patients who had failed other TNF inhibitors. However given the studies did not test this scenario and that other TNF inhibitors do not contain this restriction then it would be acceptable to not require this aspect. The sponsor has also requested a statement in relation to the RA indication that golimumab can be used in patients who had previously used TNF inhibitors. Although the GO-AFTER trial showed benefit in patients who had used TNF inhibitors previously, these patients discontinued their TNF inhibitor for a variety of reasons and did not discontinue necessarily due to failure of the TNF inhibitor. Therefore, the proposed added sentence to the RA indication that golimumab can be used in patients who had previously used TNF inhibitors should not be accepted.

Ankylosing spondylitis: The efficacy of monotherapy golimumab using accepted efficacy endpoints as per the EU guideline was demonstrated in a single pivotal trial of patients for 24 weeks with an inadequate response to NSAIDS, using the standard endpoint of ASAS20 along with improvements in physical function (BASFI). Improvements were also seen in chest expansion, haemoglobin levels, quality of life (physical component), sleep assessment and pharmacodynamic parameters but no improvement was seen in mobility (BASMI). Efficacy was seen from week 4 and maintained to week 24 but there was no difference between 50mg and 100mg doses. Results were greater in those with elevated CRP. No data is presented or claimed in relation to benefits on inhibiting structural damage. The data only included patients with moderate to severe disease and

those who had responded inadequately to NSAIDs. Other registered TNF inhibitors for ankylosing spondylitis do not restrict the indication by severity of disease or by prior therapies.

Psoriatic Arthritis: The efficacy of golimumab using accepted efficacy endpoints as per the EU guideline was demonstrated in a single pivotal trial of patients for 24 weeks with an inadequate response to DMARDs, using the standard endpoints of ACR20 / 50 / 70 along with improvements in physical function (HAQ). Efficacy was maintained to week 52. Improvements were also seen in psoriasis, quality of life (physical component), CRP levels, DAS28 responders, morning stiffness, enthesitis, haemoglobin and pharmacodynamic parameters on golimumab compared with placebo. Results were similar with or without methotrexate use and there was no dose response seen between 50mg and 100mg golimumab. No data is presented or claimed in relation to benefits on inhibiting structural damage. The data only included patients with moderate to severely active disease and other TNF inhibitors are registered for patients with active and progressive disease. The latter terminology is suggested for the indication.

Rheumatoid arthritis: The efficacy of golimumab using accepted efficacy endpoints as per the EU guideline was assessed in four trials. The first one (C0524T02) using 50mg golimumab+MTX did not demonstrate a benefit over MTX alone, although the 100mg dose did for 2 week dosing. The second trial (GO-BEFORE) did not demonstrate clear superiority of golimumab with methotrexate over methotrexate alone in methotrexate naïve patients but trended in favour of golimumab. Although the 50mg golimumab +MTX appeared to suggest a significant advantage over MTX ($p=0.042$), this may not be the case given that the primary endpoint was not significant. This was also agreed by the sponsor in their draft PI, page 4 of the Clinical Trials section. Non-inferiority assessment was conducted as a secondary analysis and suggested non-inferiority but given this was not the primary endpoint then this should be confirmed in a subsequent study. The indication wording of, "The treatment of active rheumatoid arthritis in adult patients not previously treated with MTX" should therefore be deleted. The third trial (GO-FORWARD) showed a significant benefit for golimumab+MTX over MTX but no significant difference for golimumab vs. MTX, although it trended to favour golimumab. The forth trial (GO-AFTER) showed superiority of golimumab over placebo, with better results if also on MTX. Both GO-BEFORE and GO-FORWARD showed maintenance of efficacy to week 52. Overall, the clinical trial data only included patients who had moderate to severe rheumatoid arthritis, therefore the indication should reflect this group. Abbreviations in the indication should be replaced with words.

Physical function: The inclusion of clinical endpoint claims such as those referring to physical function, although noted in the trials above, are better placed in the Clinical Trials section than the Indications.

Data issues: No studies have been conducted in the paediatric population, in those with renal or hepatic insufficiency or in examining radiological changes in the three diseases. No active comparator studies were conducted in ankylosing spondylitis or psoriatic arthritis. No studies directly compared this TNF inhibitor with other TNF inhibitors or DMARDS other than methotrexate.

Summary: The safety and efficacy of golimumab have been satisfactorily demonstrated in clinical trials submitted up to 52 weeks using an adequate exposure of patients for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (24 weeks only). No additional benefit was seen from a 100mg dose and the sponsor is not applying for this dose. The safety profile was largely as expected for a TNF inhibitor. The indications require some amendments to reflect the clinical trials submitted. As a TNF inhibitor, the risks known for this class of drugs would also apply to golimumab and appropriate warnings in the PI are required. Risks associated with TNF inhibitors include: infections, serious infections, opportunistic infections, tuberculosis, malignancies, autoimmune disorders, neurological disorders, hepatotoxicity, hypersensitivity

reactions, haematological events and congestive cardiac failure. A risk management plan should be implemented for the product.

The Delegate proposed that the registration be approved with the following indications:

Rheumatoid arthritis (RA): Simponi, in combination with methotrexate, is indicated for the treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease modifying anti rheumatic drug (DMARD) therapy, including methotrexate, has been inadequate.

Psoriatic arthritis (PsA): Simponi, alone or in combination with methotrexate, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug (DMARD) therapy has been inadequate.

Ankylosing spondylitis (AS): Simponi is indicated for the treatment of active ankylosing spondylitis in adult patients.

Evaluation Committee

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, agreed with the Delegate's proposal, but with an additional sentence in the psoriatic arthritic indication, namely: *Simponi has also been shown to improve physical functioning.*

ADEC recommended that the specific conditions of registration should include:

- that the sponsor agrees to implement a Risk Management Plan in Australia, the content of which will be agreed with TGA. This plan must include monitoring for infections, malignancies and hepatic adverse events, and
- that the sponsor provides TGA with timelines for the provision of paediatric study data.

The Committee additionally noted the sponsor's commitment to addressing all aspects of the FDA safety alert in respect of paediatric malignancies once negotiations with FDA on this issue are completed.

Outcome

Based on review of quality, safety and efficacy data, TGA approved this application by Schering Plough Pty Ltd to register Simponi solution for injection pre-filled syringe containing golimumab (rmc) 50 mg and Simponi Smartject Injector solution for injection pre-filled pen containing golimumab (rmc) 50 mg for the following indications:

> *Rheumatoid arthritis (RA): Simponi, in combination with methotrexate, is indicated for the treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease modifying anti rheumatic drug (DMARD) therapy, including methotrexate, has been inadequate.*
>
> *Psoriatic arthritis (PsA): Simponi, alone or in combination with methotrexate, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease modifying anti rheumatic drug (DMARD) therapy has been inadequate. Simponi has also been shown to improve physical function.*
>
> *Ankylosing spondylitis (AS): Simponi is indicated for the treatment of active ankylosing spondylitis in adult patients.*

Particular conditions of registration included batch release conditions as noted in this document and

- The implementation of the Simponi Risk Management Plan in Australia, the content of which which will be agreed with TGA. This plan must include monitoring for infections, malignancies and hepatic adverse events.
- Provision of paediatric study data by the 4th quarter of 2013, or as otherwise agreed with the TGA.

Attachment 1. Product Information

SIMPONI®

Solution for Injection in a pre-filled syringe

Solution for Injection in a pre-filled pen, SmartJect®

PRODUCT INFORMATION

NAME OF THE MEDICINE

Golimumab (rmc)

DESCRIPTION

Each 0.5 mL single-use pre-filled syringe or pre-filled pen contains 50 mg of golimumab. The solution is clear to slightly opalescent, colourless to light yellow. Inactive Ingredients: Sorbitol, histidine, histidine hydrochloride monohydrate, polysorbate 80 and water for injections.

PHARMACOLOGY

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

Pharmacodynamics

The binding of human TNF by golimumab was shown to neutralise TNF-induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

SIMPONI was effective in modulating select markers of inflammation and bone metabolism across indications. Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with SIMPONI resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNFα were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial SIMPONI administration and were generally sustained through weeks 14 and/or 24. SIMPONI with or without methotrexate (MTX) resulted in significant changes in serum levels of select markers of bone metabolism [increases in osteocalcin and procollagen type I N-terminal propeptide (PINP) and decreases in deoxy-pyridinolin (DPD) levels] at week 4.

Pharmacokinetics

Following subcutaneous (SC) administration of SIMPONI to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A SC injection of 50 mg golimumab to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/mL. Golimumab exhibited dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous (IV) dose. Following a single IV administration over the same dose range in patients with RA, mean systemic clearance of golimumab was estimated to be 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg, which indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be 12 ± 3 days in healthy subjects and patients with RA, PsA or AS. Following a single SC injection of 100 mg, the absorption of SIMPONI was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since SIMPONI exhibited approximately dose proportional pharmacokinetics following a SC administration, the absolute bioavailability of the SIMPONI 50 mg dose is expected to be similar to the 100 mg dose.

When 50 mg SIMPONI was administered SC to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by week 12. With concomitant use of MTX, treatment with 50 mg SIMPONI SC every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 μg/mL in patients with active PsA and approximately 0.6 μg/mL in patients with AS. Patients with RA, PsA and AS treated with SIMPONI 50 mg and MTX had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of golimumab, respectively, compared with those treated with SIMPONI 50 mg without MTX. The presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% (see CLINICAL TRIALS, “Immunogenicity”). Population pharmacokinetic analysis in patients with RA also indicated that concomitant use of MTX could reduce the apparent clearance of golimumab by 17.1%. However, concomitant use of non-steroidal anti-inflammatory drugs, oral corticosteroids or sulfasalazine (SSZ) were not found to influence the apparent clearance of golimumab.

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

Patients who developed anti-golimumab antibodies generally had increased clearance and low trough steady-state serum concentrations of golimumab (see CLINICAL TRIALS, "Immunogenicity").

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

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

CLINICAL TRIALS

Rheumatoid arthritis

The efficacy and safety of SIMPONI were evaluated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1,500 patients ≥18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg, with or without MTX, every 4 weeks. Placebo-controlled efficacy data were collected and analysed through week 24.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX. This study excluded patients who previously received TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure (CHF), demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo + MTX (n=133), SIMPONI 50 mg + MTX (n=89), SIMPONI 100 mg + MTX (n=89) or SIMPONI 100 mg monotherapy + placebo (n=133). The use of disease-modifying anti-rheumatic drugs (DMARDs) including sulfasalazine (SSZ), hydroxychloroquine (HCQ), cytotoxic agents, or other biologicals was prohibited.

GO-AFTER evaluated 461 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. This study excluded patients with serious or chronic infections, history of CHF, demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo (n=155), SIMPONI 50 mg (n=153), or SIMPONI 100 mg

(n=153). Patients were allowed to continue concomitant DMARD therapy with MTX, SSZ, and/or HCQ during the study. Discontinuation of prior anti-TNF therapies could have been for reasons including lack of efficacy (58%), intolerance (17%), and/or reasons other than safety or efficacy (40%). Other than MTX, SSZ, and HCQ, the use of other DMARDs including cytotoxic agents or other biologics was prohibited.

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve. This study excluded patients who previously received TNF blocking agents, and patients with serious or chronic infections, history of CHF, demyelinating disorders or history of malignancy with exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo + MTX (n = 160), SIMPONI 50 mg + MTX (n = 159), SIMPONI 100 mg + MTX (n = 159) or SIMPONI 100 mg monotherapy + placebo (n = 159). For patients receiving active MTX, MTX was administered at a dose of 10 mg/week beginning at week 0 and increased to 20 mg/week by week 8. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

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

The co-primary endpoint in GO-FORWARD and the primary endpoint in GO-AFTER was the percentage of patients achieving an ACR 20 response at week 14. The other co-primary endpoint in GO-FORWARD was the improvement from baseline in the Health Assessment Questionnaire (HAQ) score at week 24. The primary endpoint for GO-BEFORE was the percentage of patients achieving ACR 50 response at week 24. In addition to the primary endpoint(s), additional assessments of the impact of SIMPONI treatment on the signs and symptoms of arthritis, physical function and health-related quality of life were performed.

Key results for the 50 mg dose are shown in Tables 1 and 2 below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens. In GO-FORWARD and GO-BEFORE, the SIMPONI 100 mg monotherapy groups were not statistically different from the MTX monotherapy groups in ACR response.

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

Table 1: Key efficacy outcomes from GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX	GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)	GO-BEFORE Active RA, MTX Naïve

	Placebo + MTX	SIMPONI 50 mg + MTX	Placebo	SIMPONI 50 mg	Placebo + MTX	SIMPONI 50 mg + MTX
N[a]	133	89	155	153	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	17%	34%*	49%	62% p=0.028
ACR 50						
Week 14	10%	35%*	7%	16% p=0.006	NA	NA
Week 24	14%	37%*	5%	18%*	**29%**	**40% p=0.042[b]**
ACR 70						
Week 14	4%	14% p=0.008	2%	11% p=0.002	NA	NA
Week 24	5%	20%*	3%	12% p=0.004	16%	24% p=0.064

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

*: $p \leq 0.001$

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

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

In GO-FORWARD and GO-AFTER all individual components of the ACR response criteria [number of tender and swollen joints, patient's assessment of pain, patient's and physician's global assessment of disease activity, disability index (as measured by HAQ) and CRP] were significantly improved in the SIMPONI-treated patients versus control patients ($p < 0.001$). The results of the components of the ACR response criteria are shown in Table 2.

Table 2: Percent improvement in components of ACR Response in RA trials GO-FORWARD, GO-AFTER and GO-BEFORE

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	SIMPONI 50 mg + MTX*	Placebo	SIMPONI 50 mg*	Placebo + MTX	SIMPONI 50 mg + MTX
N[a]	133	89	155	153	160	159
Number of swollen joints						
Baseline	12.0	13.0	14	14	11	13
Week 14	38 %	62 %	22 %	44 %	NA	NA
Week 24	32 %	72 %	3 %	40 %	67 %	76 % (p=0.127)
Number of tender joints						
Baseline	21.0	26.0	26	27	26	26
Week 14	30 %	60 %	6 %	34 %	NA	NA
Week 24	21 %	62 %	-5 %	39 %	57 %	67 % (p=0.023)
Patient's assessment of pain						
Baseline	5.7	6.1	7	6.9	7	7
Week 14	18 %	55 %	10 %	26 %	NA	NA
Week 24	15 %	50 %	6 %	27 %	44 %	52 % (p=0.028)
Patient's global assessment of disease activity						
Baseline	5.3	6.0	6.5	6.8	6	6
Week 14	15 %	45 %	8 %	33 %	NA	NA
Week 24	17 %	48 %	4 %	24 %	37 %	50 % (p=0.042)
Physician's global assessment of disease activity						
Baseline	5.7	6.1	6.3	6.3	6	6
Week 14	35 %	55 %	10 %	39 %	NA	NA
Week 24	39 %	62 %	13 %	41 %	63 %	67 % (p=0.206)
HAQ score						
Baseline	1.25	1.38	1.75	1.63	1.50	1.50
Week 14	10 %	29 %	0 %	13 %	NA	NA
Week 24	7 %	31 %	0 %	13 %	37 %	44 % (p=0.141)
CRP (mg/L)						
Baseline	8.0	10.0	10.0	8.0	14.0	13.0
Week 14	2 %	44 %	0 %	33 %	NA	NA
Week 24	0 %	39 %	0 %	14 %	43 %	57 % (p=0.002)

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

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving SIMPONI 50 mg than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Physical function and health-related quality of life: In GO-AFTER and GO-FORWARD, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to week 24: 0.25 vs. 0.05 in GO-AFTER, 0.47 vs. 0.13 in GO-FORWARD, respectively. Also in GO-AFTER and GO-FORWARD, the SIMPONI 50 mg

groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at week 24: 44% vs. 28%, 65% vs. 35%, respectively.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with SIMPONI versus placebo.

Psoriatic arthritis

The safety and efficacy of SIMPONI were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). The median duration of PsA disease was 5.1 years. This study excluded patients previously treated with TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure, demyelinating disorders or a history of malignancy with the exception of treated basal skin cancer. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg, with or without MTX, every 4 weeks. Patients were randomly assigned to placebo (n=113), SIMPONI 50 mg (n=146), and SIMPONI 100 mg (n=146). The primary endpoint was the percentage of patients achieving ACR 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 3 below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens.

Table 3: Key efficacy outcomes from GO-REVEAL

	Placebo	SIMPONI 50 mg*
N[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9 %**	**51 %**
Week 24	12 %	52 %
ACR 50		
Week 14	2 %	30 %
Week 24	4 %	32 %
ACR 70		
Week 14	1 %	12 %
Week 24	1 %	19 %
PASI 75[b]		
Week 14	3 %	40 %
Week 24	1 %	56 %
HAQ Baseline score		
Median	1.00	1.00
Improvement in HAQ		

	Placebo	SIMPONI 50 mg*
Week 14 and 24 Median	0.00	0.25

*: $p < 0.05$ for all comparisons; p-value calculations are based on comparisons of median values for continuous variables
a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint
b: Based on the subset of patients with ≥ 3% body surface area (BSA) involvement at baseline

Improvements in key measures of disease activity were observed at the first assessment (week 4) after the initial SIMPONI administration and were maintained through week 24. Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes including polyarticular arthritis with no rheumatoid nodules, asymmetric peripheral arthritis, DIP arthritis, and spondylitis with peripheral arthritis. The number of patients with arthritis mutilans was too small to allow meaningful assessment. Responses observed in the SIMPONI-treated groups were similar in patients receiving and not receiving concomitant MTX.

Improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the SIMPONI-treated patients.

SIMPONI treatment resulted in significant improvement in physical function as assessed by HAQ, 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.

Ankylosing spondylitis

The safety and efficacy of SIMPONI were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a visual analog score (VAS) for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had symptoms of active disease despite current or previous NSAID or DMARD therapy. The median duration of AS disease was 5.6 years. Patients with complete ankylosis of the spine were excluded from study participation. This study also excluded patients previously treated with TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure, demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancer. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Patients were randomly assigned to placebo (n=78), SIMPONI 50 mg (n=138) and SIMPONI 100 mg (n=140). The primary endpoint was the percentage of patients achieving a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS 20) response criteria at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

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

Table 4: Key efficacy outcomes from GO-RAISE

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

*: $p \leq 0.001$ for all comparisons
a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Compared with placebo, SIMPONI treatment resulted in a significant improvement in signs and symptoms as demonstrated by the ASAS and BASDAI scores at weeks 14 and 24. Patients treated with SIMPONI achieved significantly greater improvement in all ASAS 20 components compared with placebo. Improvements in key measures of disease activity were observed at the first assessment (week 4) after the initial SIMPONI administration and were maintained through week 24. Consistent efficacy was seen in patients regardless of HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

SIMPONI treatment resulted in significant improvements in physical function as assessed by changes from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) at weeks 14 and 24. Median improvement in BASFI at week 14 was 1.4 in the SIMPONI 50 mg group, compared with worsening by 0.1 in the placebo group ($p < 0.001$). The improvement in physical function was maintained through week 24 in SIMPONI-treated patients. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24.

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

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

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

INDICATIONS

Rheumatoid arthritis (RA)
SIMPONI, in combination with methotrexate, is indicated for:

The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate.

Psoriatic arthritis (PsA)
SIMPONI, alone or in combination with methotrexate, is indicated for:

The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. SIMPONI has also been shown to improve physical function.

Ankylosing spondylitis (AS)
SIMPONI is indicated for:

The treatment of active ankylosing spondylitis in adult patients.

CONTRAINDICATIONS

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

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

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

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

PRECAUTIONS

Infections
Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported with TNF-blockers. Patients have frequently presented with disseminated rather than localised disease, and were often taking concomitant immunosuppressants such as methotrexate (MTX) or corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a

higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended (see CONTRAINDICATIONS and PRECAUTIONS, “Interactions with other medicines”).

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

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

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

Invasive Fungal Infections
For SIMPONI-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

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

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

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

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

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

Hepatitis B virus reactivation

The use of TNF-blockers including SIMPONI has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e. surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

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

Malignancies

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

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

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

Leukaemia
Cases of acute and chronic leukaemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukaemia.

Malignancies other than lymphoma
In the controlled portions of the SIMPONI Phase 2 and Phase 3 clinical trials in RA, PsA, and AS, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the SIMPONI and the control groups.

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

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking.

Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

Congestive Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers. Cases of CHF in patients with known cardiovascular risk factors have been observed with SIMPONI. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalisation or increased mortality. SIMPONI has not been studied in patients with a history of CHF and SIMPONI should be used with caution in patients with CHF. If a decision is made to administer SIMPONI to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear.

Neurological events

Use of TNF-blocking agents, including SIMPONI, has been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of SIMPONI therapy.

Haematological cytopaenias

There have been post-marketing reports of pancytopaenia, leukopaenia, neutropaenia, aplastic anaemia, and thrombocytopaenia in patients receiving TNF-blockers. Cytopaenias including pancytopaenia, have been infrequently reported with SIMPONI in clinical trials. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of SIMPONI therapy should be considered in patients with confirmed significant haematological abnormalities.

Concurrent administration of SIMPONI with anakinra

Serious infections and neutropaenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. Therefore, the combination of SIMPONI and anakinra is not recommended (see CONTRAINDICATIONS and PRECAUTIONS, “Interactions with other medicines”).

Concurrent administration of SIMPONI with abatacept

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

Surgery

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

Immunosuppression

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

Vaccinations

Patients treated with SIMPONI may receive concurrent vaccinations, except for live vaccines. No data are available on the response to vaccination, risk of infection or transmission of infection with the administration of live vaccines to patients receiving SIMPONI. Psoriatic arthritis patients treated with SIMPONI in one Phase 3 PsA study were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine. Similar numbers of psoriatic arthritis patients receiving SIMPONI and not receiving SIMPONI had at least a 2-fold increase in antibody titres. The proportions of patients with response to pneumococcal vaccine were lower among SIMPONI and control-treated patients receiving MTX compared with patients not receiving MTX. Overall, the data indicate that SIMPONI does not suppress the humoral immune response to this vaccine.

Allergic reactions

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

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

Autoimmunity
Treatment with SIMPONI may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms of a lupus-like syndrome following treatment with golimumab, treatment should be discontinued (see ADVERSE EFFECTS, “Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies”).

Use in children and adolescents
Specific studies of SIMPONI in paediatric patients have not been conducted.

Use in the elderly
In the Phase 3 studies in RA, PsA, and AS, no overall differences in adverse effects (AEs), serious adverse effects (SAEs), and serious infections in patients age 65 or older (N=155) who received SIMPONI were observed compared with younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

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

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

Use in Pregnancy (Category C)
The use of SIMPONI in pregnant women is not recommended. Women of childbearing potential should be advised to use adequate contraception and continue its use for at least 6 months after the last SIMPONI treatment. Studies in cynomolgus monkeys have shown no untoward effects on the course of pregnancy, embryofoetal development, parturition or neonatal development, at doses achieving serum concentrations in excess of those expected with the recommended dose.

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

Genotoxicity
No genotoxicity tests have been conducted with golimumab.

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

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

Interactions with other medicines
No interaction studies have been performed.

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

Live vaccines
Live vaccines should not be given concurrently with SIMPONI (see PRECAUTIONS).

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

ADVERSE EFFECTS

Safety data from Phase 2 and 3 clinical trials are available from 2578 SIMPONI-treated patients including 1600 with RA, 394 with PsA, 353 with AS, and 231 with severe persistent asthma.

Table 5 summarises the adverse drug reactions that occurred at a rate equal to or higher than 1% in SIMPONI groups and at a frequency higher than the placebo group during the

placebo-controlled period of the Phase 3 studies in RA, AS and PsA, respectively (in 639 placebo and 1659 golimumab exposed patients).

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

Table 5: Adverse Drug Reactions Reported by ≥ 1% of Patients in the Phase 3 Trials of RA, PsA and AS through week 16[a]

	Placebo ± DMARDs N=639	SIMPONI ± DMARDs N=1659
Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)	92 (14%)	279 (17%)
Bacterial infections (such as cellulitis)	6 (1%)	24 (1%)
Viral infections (such as influenza and herpes)	20 (3%)	75 (5%)
Bronchitis	9 (1%)	31 (2%)
Sinusitis	8 (1%)	27 (2%)
Superficial fungal infections	8 (1%)	31 (2%)
Anaemia	6 (1%)	20 (1%)
Allergic reactions (bronchospasm, hypersensitivity, urticaria)	7 (1%)	24 (1%)
Depression	6 (1%)	18 (1%)
Insomnia	7 (1%)	22 (1%)
Dizziness	8 (1%)	33 (2%)
Paraesthesia	3 (1%)	27 (2%)
Headache	36 (6%)	75 (5%)
Hypertension	10 (2%)	51 (3%)
Constipation	2 (0%)	18 (1%)
Dyspepsia	10 (2%)	38 (2%)
Gastrointestinal and abdominal pain	17 (3%)	56 (3%)
Alanine aminotransferase increased	18 (3%)	58 (4%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Alopecia	4 (1%)	18 (1%)
Dermatitis	7 (1%)	17 (1%)
Pruritus	10 (2%)	33 (2%)
Rash	15 (2%)	48 (3%)
Pyrexia	4 (1%)	20 (1%)

	Placebo ± DMARDs N=639	SIMPONI ± DMARDs N=1659
Asthenia	22 (3%)	70 (4%)
Injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia)	14 (2%)	97 (6%)
Chest discomfort	7 (1%)	17 (1%)

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

Less common clinical trial adverse drug reactions (<1%)
Adverse drug reactions that occurred at rates less than 1% during the SIMPONI clinical trials included the following events listed by system organ class:

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

Neoplasms benign, malignant and unspecified: Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus), lymphoma, paediatric malignancy*, leukaemia*

Investigations: Neutrophil count decreased

Blood and lymphatic system disorders: Leukopaenia, thrombocytopaenia, pancytopaenia, aplastic anaemia*

Endocrine disorders: Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)

Metabolism and nutrition disorders: Blood glucose increased, lipids increased

Nervous system disorders: Demyelinating disorders, balance disorders, dysguesia

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

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

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

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

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

Hepatobiliary disorders: Cholelithiasis, hepatic disorders

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

Musculoskeletal and connective tissue disorders: Lupus-like syndrome

Renal and urinary disorders: Bladder disorders, renal disorders

Reproductive system and breast disorders: Breast disorders, menstrual disorders

General disorders and administration site conditions: Impaired healing

Injury, poisoning and procedural complications: Bone fractures

[*Observed with other TNF-blockers, but not observed in clinical studies with golimumab].

Infections (see PRECAUTIONS)
Upper respiratory tract infection was the most common adverse reaction reported in the combined Phase 3 RA, PsA and AS studies through week 16, occurring in 7.2% of SIMPONI-treated patients (incidence per patient-year: 0.26; 95% CI: 0.22, 0.31) as compared with 5.8% of control patients (incidence per patient-year: 0.23; 95% CI: 0.17, 0.31). The incidence per patient-year (95% confidence interval; CI) of upper respiratory tract infections through 1 year of follow-up was 0.23 events (0.21, 0.25) for SIMPONI-treated patients and 0.25 events (0.20, 0.31) for control patients.

In controlled Phase 3 trials through week 16 in RA, PsA, and AS, infections were observed in 28.3% of SIMPONI-treated patients (incidence per patient-year: 1.28; 95% CI: 1.18,

1.38) compared with 24.7% of control patients (incidence per patient-year: 1.17; 95% CI: 1.02, 1.33). The incidence per patient-year (95% CI) of infections through 1 year of follow-up was 1.32 events (1.27, 1.38) for SIMPONI-treated patients and 1.31 events (1.18, 1.44) for control patients.

In controlled Phase 3 trials through week 16 in RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI-treated patients (incidence per patient-year: 0.06; 95% CI: 0.04, 0.08) and 1.3% of control treated patients (incidence per patient-year: 0.04; 95% CI: 0.02, 0.08). Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, and tuberculosis. The incidence per patient-year (95% CI) of serious infections through 1 year of follow-up was 0.05 events (0.04, 0.06) for SIMPONI-treated patients and 0.06 events (0.04, 0.09) for control patients.

Malignancies (see PRECAUTIONS)

Lymphoma

The incidence of lymphoma in SIMPONI-treated patients with RA, PsA and AS during the controlled portions of Phase 2b and Phase 3 clinical trials, and through 1 year of follow-up, was higher than expected in the general population. Lymphoma was diagnosed in 2 subjects (both in golimumab 100 mg treatment groups) with an incidence (95%, CI) per 100 subject-years of follow-up of 0.10 (0.01, 0.37) events for golimumab and 0.00 (0.00, 0.90) events for placebo.

Malignancies other than lymphoma

In the controlled portions of the SIMPONI Phase 2 and Phase 3 clinical trials in RA, PsA, and AS, and through 1 year of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the SIMPONI and the control groups.

Through 1 year of follow-up of the Phase 2b and Phase 3 studies in rheumatologic indications, non-melanoma skin cancer was diagnosed in 19 subjects (5 in placebo, 6 in golimumab 50 mg and 8 in golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.72 (0.39, 1.20) events for golimumab and 1.51 (0.49, 3.52) events for placebo.

Through 1 year of follow-up, of the Phase 2b and Phase 3 studies in rheumatologic indications, malignancies besides non-melanoma skin cancer and lymphoma were diagnosed in 12 subjects (2 in placebo, 6 in golimumab 50 mg and 4 in golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.51 (0.24, 0.94) events for golimumab and 0.60 (0.07, 2.17) events for placebo.

Cases reported in clinical studies in asthma

In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through week 52. Eight malignancies were reported in the combined

golimumab treatment group (n=230) and none in the placebo treatment group (n=79). Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

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

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

Liver enzyme elevations

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

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials through week 16, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of SIMPONI and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS study, more SIMPONI-treated patients (25.6%) than control patients (3.9%) had mild ALT elevations. Through 1 year of follow-up, the incidence of mild ALT elevations was similar in the SIMPONI-treated and control patients in the RA and PsA studies. In the AS study, the incidence of mild ALT elevations was higher in SIMPONI-treated patients than in control patients.

In the RA and AS studies through week 16, ALT elevations $\geq$ 5 x ULN were uncommon and seen in more SIMPONI-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. Through 1 year of follow-up, the incidence of ALT elevations ≥ 5 x ULN was similar in both SIMPONI-treated and control patients in the Phase 3 RA, PsA and AS studies. The majority of these elevations were asymptomatic.

Hepatobiliary adverse events

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

Psoriasis: New-Onset and Exacerbations

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including SIMPONI. Cases of

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

Injection site reactions

In controlled Phase 3 trials through week 16 in RA, PsA and AS, 5.8% of SIMPONI-treated patients had injection site reactions compared with 2.2% in control patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

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

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

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

In Phase 3 trials in RA, PsA, and AS at 1 year of follow-up, 4.0% of SIMPONI-treated patients and 2.6% of control patients were newly ANA-positive (at titres of 1:160 or greater) compared with baseline. The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients with anti-dsDNA negative at baseline was uncommon.

DOSAGE AND ADMINISTRATION

Rheumatoid arthritis

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

Psoriatic arthritis

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

Ankylosing spondylitis

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

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

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

Elderly patients (≥ 65 years)

No dosage adjustment is required in the elderly.

Paediatric patients (< 18 years)

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

Patients with impaired renal and/or hepatic function

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

Instructions for administration and disposal

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

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

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

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

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

OVERDOSAGE

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

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

PRESENTATION AND STORAGE CONDITIONS

SIMPONI pre-filled syringe

SIMPONI is supplied as a sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. The needle shields are manufactured from dry natural rubber containing latex (see PRECUATIONS, “Allergic reactions”). SIMPONI is available in packs of 1 or 3* pre-filled syringe(s).

SIMPONI SmartJect injector pen

SIMPONI is supplied as a sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. This syringe is contained in a single-use pre-filled pen called “SmartJect”. The needle shields are manufactured from dry natural rubber containing latex (see PRECAUTIONS, “Allergic reactions”). SIMPONI is available in packs of 1 or 3* pre-filled pen(s).

* Not currently supplied in Australia.

Storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not shake. Keep the pre-filled pen/syringe in the outer carton in order to protect it from light.

NAME AND ADDRESS OF SPONSOR

Schering-Plough Pty Limited

Level 4, 66 Waterloo Road

North Ryde NSW 2113

AUSTRALIA

Manufactured by:
Centocor B.V.
Leiden, The Netherlands

POISON SCHEDULE OF MEDICINE

S4 – Prescription Only Medicine

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 06 November 2009.

Version 1