Doc.Ref.: EMEA/446762/2009

ASSESSMENT REPORT

FOR

Simponi

International Nonproprietary Name: golimumab

Procedure No. EMEA/H/C/000992

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Centocor B.V. submitted on 3 March 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Simponi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The applicant applied for the following indication:

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 including MTX 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 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 disease-modifying anti-rheumatic drug (DMARD) therapy 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 when the response to conventional therapy has been inadequate. Simponi has also been shown to improve physical function and health related quality of life.

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 24 March 2004, 17 March 2005 and 21 April 2005. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Tomas Salmonson
Co-Rapporteur: Pierre Demolis

1.2 Steps taken for the assessment of the product

• The application was received by the EMEA on 3 March 2008.
• The procedure started on 26 March 2008.
• The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 June 2008.
• During the meeting on 21-24 July 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2008.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2008.
- The summary report of the inspection carried out at the following site(s) Centocor BV - Einsteinweg 101 - Leiden - Netherlands between 17 March 2009 and 20 March 2009 was issued on 8 May 2009
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 November 2008.
- During the CHMP meeting on 15-18 December 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 20 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 8 June 2009.
- During the meeting on 22 – 25 June 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Simponi on 25 June 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 June 2009.

2   SCIENTIFIC DISCUSSION

2.1   Introduction

This application for Simponi concerned three indications - rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

Rheumatoid Arthritis
RA is an autoimmune disease that causes chronic inflammation of the joints. RA, which affects approximately 1% of the population, is more prevalent among women than men and usually develops in the fourth or fifth decades of life. While the exact pathogenesis of RA is still unknown, it is characterized by accumulation and activation of several cell systems such as T-cells, B-cells, macrophage- and fibroblast-like cells which produce large amounts of proinflammatory cytokines. The resulting hyperplastic synovial membrane, in conjunction with osteoclast activation, leads to the degradation of adjacent cartilage and bone. RA is typically a progressive illness that has the potential to cause joint destruction and functional disability.

The aims of antirheumatic therapy are to relieve pain, to decrease inflammatory synovitis, to improve or sustain physical function and to prevent structural damage of the joints. The use of targeted biological agents such as tumour necrosis factor alpha (TNFα) or interleukin-6 (IL-6) receptor inhibitors/antagonists has been established during the last decade. Today, a number of biological antirheumatic agents are approved in the EU for treatment of both treatment naïve patients as well as those not responding adequately to other disease-modifying antirheumatic drug (DMARD). However, there is still a medical need since about 30% of patients fail on these therapies.

Psoriatic Arthritis
PsA is a chronic, inflammatory arthritis associated with psoriasis. The prevalence of psoriasis in the general Caucasian population is approximately 2%; approximately 6% to 42% of psoriasis patients develop PsA. Affecting men and women equally, PsA typically appears between the ages of 30 and 50 years. PsA usually involves multiple peripheral joints, the axial skeleton, sacroiliac joints, fingernails, and entheses. The presentation of PsA has been categorized into 5 overlapping clinical patterns, which include oligoarthritis, polyarthritis, arthritis of distal interphalangeal (DIP) joints, spondylitis, and arthritis mutilans. While PsA has some symptoms similar to rheumatoid arthritis (RA) (e.g. joint pain and destruction and fatigue), it can be distinguished from RA by one or more factors such as presence of psoriasis; seronegativity for rheumatoid factor (RF) (> 80% of patients); patterns of joint involvement including asymmetry, distal interphalangeal disease, and spinal disease. Overall PsA and RA are closely related diseases and have similar approved products.

Ankylosing Spondylitis
AS is a chronic inflammatory disease of unknown etiology that involves the sacroiliac joints, axial skeleton, entheses, and peripheral joints. Its prevalence has been estimated to be between 0.1-1.1% of the population. Chronic inflammation of entheses leads to new bone formation, syndesmophytes, and ankylosis of joints, primarily in the axial skeleton. It is this axial ankylosis that may lead to loss of range of motion and to disability. The disease may also have nonskeletal manifestations, including uveitis, carditis, pulmonary fibrosis, and cardiac conduction abnormalities. AS belongs to the group of spondyloarthropathies and is associated with the presence of the HLA-B27 allele. Although patients may experience a variety of musculoskeletal symptoms (such as arthralgias and morning stiffness), the most common presenting symptom is low-back pain. These musculoskeletal symptoms may be associated with constitutional symptoms, such as fatigue, fever, and weight loss. Physical therapy has a positive effect on stiffness, spinal mobility and even pain. Pharmacological treatment of AS includes non-steroidal anti-inflammatory drugs (NSAID), systemic or intraarticular corticosteroids, sulfasalzine and methotrexate (MTX). More recently, TNFα-inhibitors have shown efficacy in the active disease and have been incorporated into the treatment of active moderate to severe AS patients who have had an inadequate response to conventional therapy.

TNFα is considered a key inflammatory mediator that exhibits a wide variety of functional activities. Abnormally high levels of TNFα have been implicated in the pathophysiology of several immune-mediated diseases, including RA, PsA, and AS. Binding of TNF by an anti-TNF antibody prevents the target from binding to cell surface TNF receptors, and consequently prevents downstream signaling cascades and deleterious effects of inappropriate or excessive TNF expression. Treatment with anti-TNFα agents has been demonstrated to significantly improve signs and symptoms, physical function, and health-related QOL in subjects affected by these rheumatologic disorders. Treatment with anti-TNFα agents has also been shown to inhibit structural damage in subjects affected by RA and PsA.

Golimumab (also known as CNTO 148 and rTNV148B), the active substance of Simponi, is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody. It binds with high affinity and specificity to both soluble and transmembrane forms of TNFα, thereby neutralizing the biological activity of TNFα. Golimumab is produced by a murine hybridoma cell line with recombinant DNA technology.

The application for marketing authorisation for Simponi was a full application for a new active substance. The assessment has taken into account the recommendations provided in the relevant CHMP guidelines within these respective disease areas, i.e. Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis (CHMP/EWP/438/04), Points to Consider on the Clinical Investigation of Medicinal Products other than NSAIDs in Rheumatoid Arthritis (CHMP/EWP/556/95) and the draft Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis (CPMP/EWP/4891/03).

Scientific advice has been given by the CHMP for the clinical development of golimumab in psoriatic arthritis and ankylosing spondylitis.

The initial indications proposed at the time of application were:

> *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 including MTX 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 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 disease modifying anti rheumatic drug (DMARD) therapy 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 when the response to conventional therapy has been inadequate. Simponi has also been shown to improve physical function and health related quality of life.

The approved indications are:

Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
Simponi has also been shown to improve physical function in this patient population.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Simponi has also been shown to improve physical function in this patient population.

Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Simponi is a clear to slightly opalescent, colourless to light yellow sterile solution for injection containing golimumab at 100 mg/ml. The product is supplied in pre-filled, single-use pens and syringes containing 50 mg golimumab.

In all indications, the posology is Simponi 50 mg given as a subcutaneous injection once a month, on the same date each month.

2.2   Quality aspects

Introduction

The drug substance golimumab is a recombinant human monoclonal antibody directed against both soluble and transmembrane forms of human TNFα, which prevents the binding of TNFα to its receptors, thereby neutralising its biological activity.

Golimumab is derived from a Sp2/0 cell line that has been transfected with an expression plasmid containing the genes encoding the heavy and light chains.

A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed. The drug substance is manufactured in a 9 stage process. The fermentation process uses a continuous perfusion mode in a bioreactor. The purification, from the cell culture harvest, includes a series of chromatography steps, ultra-diafiltration steps and viral inactivation and filtration steps.

The drug product is manufactured by sterile filtration, aseptic filling and stoppering of pre-filled syringes which are then assembled into a device for subcutaneous administration (single-use auto-injector or passive needle guard delivery system (UltraSafe)).

Active Substance

Nomenclature

INN Name: golimumab
Compendial Name: not applicable
USAN/JAN: golimumab
Laboratory Code Name: CNTO 148
CAS Registry Number: 476181-74-5
Other Names: Immunoglobulin G1, anti- (human tumor necrosis factor α) (human monoclonal CNTO 148 γ1-chain), disulfide with human monoclonal CNTO 148 κ-chain, dimer

Description of the active substance

Golimumab is a recombinant human monoclonal antibody of IgG1 kappa subclass composed of two heavy chains (approximately 50 kDa each) and two lights chains (approximately 24 kDa each), with 16 disulfide bonds. Golimumab contains two N-glycans.

• Manufacture

Cell culture, purification, and analytical testing of process intermediates and CNTO 148 bulk drug substance (formulated bulk) are conducted at Centocor B.V. Einsteinweg 101 2333 CB Leiden The Netherlands.

Development genetics

The cell substrate was derived from murine myeloma origin (Sp2/0-Ag14 (Sp2/0) host cells). Sp2/0 cells were transfected with two expression plasmids containing the genes encoding golimumab heavy and light chains, following by cloning and subcloning steps to select one high-producing clone.

Cell bank system

A two-tiered cell banking system of MCB and WCB has been developed and maintained in accordance to cGMP and ICH guidelines.

Seed cells corresponding to the high-producing clone were adapted to growth in a medium not containing foetal bovine serum, leading to the establishment of the original MCB and WCB. Procedures followed for the preparation of MCB and WCB were appropriately described. An extensive range of tests has been performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Fermentation process

The fermentation process corresponds to stages 1 and 2 of the drug substance manufacturing process:
- Stage 1 - preculture and expansion:
Preculture is initiated from a single WCB vial and subsequent expansion of the cell culture in culture flasks, disposable culture bags, and seed bioreactor. The cells are cultured until the cell density and volume required for inoculation of the production bioreactor are obtained.
- Stage 2: bioreactor production:
The contents of the seed bioreactor are transferred into the production bioreactor containing a chemically-defined medium. Cell culture harvest is collected from the production bioreactor while cells are retained using a cell-retention device, and the culture is replenished with fresh media.

Purification process
Purification of golimumab from the cell culture harvest is performed in stages 3 through 8:
- Stage 3: Affinity chromatography;
- Stage 4: thawing and pooling of direct product capture (DPC) eluates;

- Stage 5: Viral inactivation by solvent/detergent treatment;
- Stage 6: cation exchange chromatography;
- Stage 7: anion exchange chromatography;
- Stage 8: virus retentive filtration.

Preparation of the pre-formulated bulk and formulated bulk drug substance is performed in stage 9 which comprises an ultrafiltration step to concentrate the drug substance, a diafiltration step to add the formulation excipients and remove in-process buffer salts, and a 0.2 μm filtration.
The formulated bulk drug substance is stored at ≤ -40°C.

Manufacturing process development and process validation

Throughout development, changes have been introduced in the drug substance manufacturing process, including a new cell line, cell retention technology, elimination of animal-derived raw materials, formulation, manufacturing scale, manufacturing sites. A comprehensive process manufacturing history was provided, showing the different changes introduced, and the corresponding batches involved, as well as the use of these batches.

Process validation studies provided covers aspects of:
 i) Analysis of process consistency;
ii) Removal of process- and product-related impurities (full scale and reduced scale);
iii) Hold times and conditions for all process intermediates;
iv) Chromatography resin lifetime;
v) Reprocessing at five points in the manufacturing process;
vi) Integrity of the expression construct, authenticity of the cell line and ability to run the manufacturing process.

The approach used for process validation mainly consists of demonstrating that the process is capable of producing batches that meet all requirements with respect to in-process controls (IPC), critical quality attributes (CQA) and process parameters (PP).

Characterisation

A) Elucidation of structure and other characteristics:

A1) Physicochemical characterisation:

- Primary structure:
Expected N- and C-terminal amino acid sequences for the heavy and light chains were confirmed by Edman degradation, peptide mapping and intact molecular mass analysis. The heavy chain showed C-terminal lysine heterogeneity.
Expected internal amino acid sequences of the heavy and light chains were confirmed by peptide mapping with online mass spectrometry analysis. Post-translational modifications were identified and correspond primarily for the heavy chain to partial removal of the C-terminal lysine, N-glycosylation and deamidation. Low levels of deamidation on the heavy chain and cyclisation on the light chain were also detected.

The expected disulfide bond structure for a human IgG1 was confirmed by peptide mapping under non-reduced conditions. Two intra-chain disulfide bonds in each light chain, four intra-chain disulfide bonds in each heavy chain, and three inter-chain disulfide bonds were identified.

A low level of free sulfhydryls was detected using Ellman's reagent.

- Carbohydrate structure:
The N-linked glycan structures were determined to be biantennary, core-fucosylated oligosaccharide structures with terminal galactose and sialic heterogeneity. No galactosamine (from O-glycans) was detected.

Serial exoglycosidase digestion confirmed the structures identified by oligosaccharide analysis.

- Higher order structure:
Far-UV circular dichroism spectroscopy detected predominantly beta-sheet secondary structure, typical of IgG1 proteins. Near-UV circular dichroism spectroscopy showed spectral results characteristic of an IgG1 protein.

Sedimentation velocity analytical ultracentrifugation analysis detected mainly monomeric IgG, with small amounts of aggregates and fragments also present.

- Microheterogeneity:
Mass spectrometry analysis of the intact protein and reduced and alkylated heavy chain and light chain revealed the presence of mass microheterogeneity and identified the primary causes as N-glycosylation and C-terminal lysine heterogeneity on the heavy chain.

The charge isoforms of golimumab observed by isoelectric focusing (IEF) were identified as deamidated species containing aspartic acid and isoaspartic acid on the heavy chain, and as sialylated variants of the same species. Potency and binding affinities for isolated major charge isoforms were indistinguishable from each other and from the reference standard.
There were no substantial differences in the rates of clearance for the various glycoforms *in vivo* based on affinity capture and analysis of mass spectrometry analysis of patient samples.

A2) Biological characterisation:

Antigen-binding activity was analysed by an *in vitro* cell-based bioactivity assay and a sandwich enzyme immunoassay.
The Fc integrity, characterised with respect to FcγRI and FcRn binding, established that golimumab has a functionally intact Fc; however, Fc function is not part of the mechanism of action.
Golimumab binding affinity to human TNFα trimer was established by surface plasmon resonance and kinetic exclusion assay.

B) Impurities:

Product-related substances and impurities correspond to:
- N-glycosylation on the heavy chain;
- Removal of C-terminal Lysine on the heavy chain;
- Deamidation on the heavy chain;
- Dimeric aggregate formation;
- Hinge region cleavage.

Potential process-related impurities include cell substrate derived impurities (host cell proteins, host cell DNA, retroviruses), media components and downstream-derived impurities such as leached protein A.

- Specification

The drug substance release specifications, including tests for identity, impurities, potency, quantity and general attributes, are acceptable and well justified.

- Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance with current ICH guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.
The stability data provided were within the specifications and support the proposed shelf life when stored at ≤ -40°C.

Medicinal Product

- Pharmaceutical Development

The drug product is a solution for subcutaneous administration (50 mg/0.5 mL) supplied in a single-use pre-filled syringe. The drug product is formulated with L-histidine, sorbitol, polysorbate 80 and water for injections. These excipients are commonly used in formulating protein pharmaceuticals.
The pre-filled syringe is assembled into either an auto-injector (called SmartJect) or a passive needle guard delivery system (called UltraSafe).

Throughout drug product development, changes have been introduced, including a new formulation, primary container and manufacturing site.
These different changes were supported by several comparability studies.

- Adventitious Agents

No animal-derived raw materials were used in the preparation of the MCB or WCBs and in the manufacturing of Simponi. Only cells prior to the Research Cell Bank (RCB) were cultivated with foetal bovine serum (FBS). Data were provided to support the use of FBS. MCB, WCBs, host cell lines and end-of-production cells were tested for bovine viruses and no contamination was detected. Safety concerning TSE is considered sufficiently assured.
Control of potential contamination by other non-viral adventitious agents (mycoplasma, bioburden, endotoxin) was considered adequate.

Extensive screening for viruses was performed. Raw material controls minimise the risk of viral contamination, and clearance studies provide assurance that any potential virus will be removed or inactivated by the manufacturing process (solvent/detergent virus inactivation step and virus removal filtration step in addition to the viral clearance achieved through orthogonal chromatographic unit operations (Protein A chromatography and anion exchange chromatography)).

- Manufacture of the product

The frozen formulated bulk drug substance is thawed, pooled, mixed, sterile filtered (0.2 μm) and aseptically filled into sterile 1 mL Type 1 borosilicate glass syringes stoppered with a tetra fluoroethylene polymer coated butyl rubber stopper. These operations take place at Baxter Pharmaceutical Solutions, USA.
The pre-filled syringes are shipped to Cilag AG, Switzerland and assembled into a needle safety device (UltraSafe Passive Safety System) or in a pre-filled pen (Centocor Autoinjector / SmartJect).

The drug product manufacturing process is monitored by process variables, including both inputs (i.e. process parameters) and outputs (i.e. process monitoring) that are controlled throughout the manufacturing process to ensure both process and product consistency.

Manufacture of the pre-filled syringe and its assembly into a device has been validated. Process validation provided a documented, thorough understanding of the ability of the manufacturing process to consistently and reliably meet predetermined product specifications and quality attributes.

Drug product characterisation was performed on validation batches and includes a comprehensive analysis of primary structure, carbohydrate structure, higher order structure, heterogeneity, purity, biological function, and particulate matter. These studies show similar variants as described for the drug substance.

- Product specifications

The drug product specifications include control of the product in the pre-filled syringe, the pre-filled syringe in the pen and the pre-filled syringe in the UltraSafe delivery system, and contain tests for identity, impurities, potency, quantity, device functionality and general attributes.

- Stability of the Product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of drug product. On the basis of the data provided, the approvable shelf life for the drug product is one year at 2-8°C.

Discussion on chemical, pharmaceutical and biological aspects

The generation of the original cell line, from the expression construct to the selection process was well described. Cell banks have been established and adequately characterised.

The drug substance manufacturing process was well described. Issues raised during the evaluation procedure on the validation and control strategy were adequately addressed by the Applicant. Sufficient in-process controls are in place and the proposed acceptance criteria are considered acceptable.

Process validation for the drug substance manufacturing process was considered acceptable.

Thorough characterisation studies were reported, where the applicant has used state-of-the-art techniques in the analyses of primary structure, oligosaccharide structure, higher order structure, microheterogeneity, purity and impurities, biological function, degradation pathways.

The proposed shelf life for the drug substance was considered acceptable.

The pharmaceutical development of the drug product was considered satisfactory.

The drug product manufacturing process was adequately described. Appropriate controls and acceptance criteria are in place. Process validation was considered acceptable.

The description and validation of analytical procedures for the drug substance and drug product were generally satisfactory except for certain methods for which additional information was requested. These issues have been solved.

Most of the issues identified during the evaluation procedure on the control of the drug substance and setting of specifications also applied to the drug product. All the concerns were considered resolved. The Applicant has revised the drug substance and drug product specifications; the acceptance criteria for most tests have been tightened and are acceptable.

On the basis of the stability data provided, a shelf life of 12 months at 2-8°C for the drug product is considered acceptable.

Viral safety and safety concerning other adventitious agents including TSE are sufficiently assured. To further confirm the robustness of the virus removal steps, the applicant will undertake a post-approval study repeating part of the validation using a small non-enveloped DNA virus.

The drug substance manufacturing site, Centocor BV in Leiden, The Netherlands, was inspected by the Dutch inspectorate in March 2009. This site operates in accordance to current EU Good Manufacturing Practices (GMP).

Except for a number of points, which will be addressed as part of post-approval follow-up measures, the overall Quality of Simponi is considered acceptable.

2.3   Non-clinical aspects

Introduction

The non-clinical testing strategy to support development of golimumab was designed and conducted in accordance with the ICH S6 guidance for the preclinical safety evaluation of biotechnology-derived pharmaceuticals. The cynomolgus monkey was chosen as the most relevant non-clinical species, since golimumab showed little or no neutralization of dog, rabbit, mouse or rat TNFα. For the studies in mice, an analogous anti-mouse TNFα monoclonal antibody designated cV1q, developed during the non-clinical testing of another TNFα inhibitor, infliximab (Remicade), was used.

Two primary pharmacodynamic studies were performed with material from the original hybridoma cell line C420A (a pharmacokinetic study and an arthritis efficacy study in a mouse). All other primary pharmacodynamic studies, safety pharmacology studies, toxicology studies and clinical trials were performed with golimumab purified from cell line C466D or C524A. The liquid formulation generated from the C524A cell line was used in all Phase 3 clinical studies and represents the formulation intended for marketing.

Relevant non-clinical studies were undertaken in accordance with GLP.

Pharmacology

- Primary pharmacodynamics

Golimumab binds with high affinity and specificity to both the soluble and transmembrane bioactive forms of TNFα. With a KD value of 18 pM the affinity of golimumab for soluble TNFα was 2.4-fold greater than infliximab (KD of 44 pM), while the affinity of both mAbs for transmembrane TNFα was similar (1.89 nM and 1.62 nM, respectively). As expected, large complexes were observed between bivalent golimumab and TNFα trimers, and in antibody excess the molecular weight of these complexes was consistent with three golimumab molecules bound to one or two TNFα trimers. Golimumab was shown to inhibit the binding of human TNFα to p55 and p75 TNFα receptor fusion protein in a competition assay format;
No binding to other representative members of the TNFα ligand superfamily (lymphotoxin alpha, lymphotoxin alpha/beta heterotrimer, TRAIL and glycocorticoid-induced TNF receptor ligand) was seen.

Golimumab potency to neutralize TNFα-mediated cellular responses was tested in three separate *in vitro* bioassays. In comparison to infliximab, golimumab showed the same, or in some experiments, a slightly higher potency.

Golimumab was most potent against human and chimpanzee TNFα (IC50 ~3 ng/ml); the IC50 for golimumab was 10-60 fold higher against baboon, rhesus, cynomolgus, pigtail macaque and dog TNFα and 400-4,300 fold higher against marmoset, cottontop tamarin, rabbit and guinea pig TNFα. No neutralization of rat or mouse TNFα by golimumab was observed. Therefore, the cynomolgus monkey was chosen as the pharmacologically and toxicologically relevant species. Using purified recombinant cynomolgus TNFα, golimumab was shown to have 34-fold less affinity and to be 72-fold less potent in neutralizing cynomolgus TNFα compared to affinity and neutralization of human TNFα.

Investigations were also performed *in vivo* in a mouse model of arthritis. A single dose of golimumab (1, 3, 10 or 30 mg/kg) significantly delayed onset of clinical symptoms compared to a vehicle control group. Histology showed golimumab dose-dependent improvement in joint architecture that was statistically significant at a dose of 30 mg/kg compared to vehicle-treated transgenic mice. Serum concentrations of GM-CSF, MCP-1, KC, G-CSF, IP-10 and IL-6 were elevated in the serum of vehicle-treated transgenic mice and reduced by treatment with golimumab.

- Secondary pharmacodynamics

No secondary pharmacodynamic studies were undertaken.

- Safety pharmacology programme

In accordance with relevant guidance documents, safety pharmacology endpoints were incorporated into the toxicology testing. No adverse effects of golimumab were observed in safety pharmacology evaluations for cardiovascular, respiratory and CNS safety following single or repeated dosing of cynomolgus monkeys via intravenous or subcutaneous administration at doses up to 50 mg/kg once or twice weekly for up to 6 months. However, the indirect measurements of blood pressure performed during the toxicology studies showed occasional large variations including unusually low values. The heart rate measured under the same conditions showed values much higher than those observed in freely moving animals. Tachycardia, here probably resulting from restraining of the animals, is well known to blunt any potential effect on rhythm disturbance or effect on cardiac repolarisation. For these reasons it seems impossible to reasonably conclude about any potential impact of golimumab on the cardiovascular system.

- Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were conducted with golimumab. Due to the high binding specificity of golimumab for its target, TNFα, it is unlikely to have pharmacodynamic interactions with co-administered drugs.

Pharmacokinetics

The majority of PK and toxicokinetic (TK) data were generated as part of the toxicology studies, to assess golimumab exposure in cynomolgus monkeys following single and multiple intravenous and subcutaneous administrations at doses ranging from 1 to 50 mg/kg. No non-clinical pharmacokinetic drug interaction studies have been performed.

Following subcutaneous or intravenous administrations in cynomolgus monkeys, golimumab displayed approximately dose-proportional pharmacokinetics. Following multiple dosing, steady state was reached after approximately 4 to 5 half-lives. After subcutaneous administration, the C_{max} was generally observed within 2 to 3 days with an absolute bioavailability of at least 77%. In general, the volume of distribution at steady state was slightly larger than the serum volumes, suggesting a distribution outside the intravascular space. When considering all absorption studies, the mean terminal half-life values ranged from 11 days to 18 days. No obvious gender differences in pharmacokinetic parameters were observed.

When golimumab was administered to pregnant monkeys, it was shown to cross the placenta and substantial golimumab exposure was observed in the foetal circulation. Golimumab was also found in monkey breast milk. These findings are reflected in the SPC.

Antibodies to golimumab were measured in non-clinical studies to support interpretation of pharmaco/toxicokinetics and toxicological observations. The incidence of antibodies to golimumab was greater at lower dose levels (3 and 10 mg/kg), than at higher dose levels (25 and 50 mg/kg). The high concentrations of circulating golimumab interfered with detection of anti-golimumab antibodies, making it difficult to determine if the immune response declined due to assay interference, whether high-dose tolerance occurred or if golimumab inhibited antibody formation. In monkeys that tested positive for anti-golimumab antibodies, accelerated CL and shortened $t_{1/2}$ were observed. It has not been established whether the formation of antibodies to golimumab differed between monkeys administered golimumab via intravenous and subcutaneous routes; however the cell line or formulation used appeared to have no obvious effect upon the immune response detected in monkeys.

Toxicology

- Single dose toxicity

No golimumab single dose toxicity study was conducted. Acute toxicity has been addressed by data from single dose PK studies and from the repeated dose toxicity studies.

- Repeat dose toxicity (with toxicokinetics)

Golimumab was evaluated in subcutaneous and intravenous repeated-dose toxicity studies using doses up to 50 mg/kg either weekly or twice weekly. Supportive toxicology studies were conducted in mice using the analogous anti-mouse TNFα monoclonal antibody, cV1q, to evaluate the effects of anti-TNFα treatment on reproductive development and chronic toxicity. The cV1q antibody has been shown to exhibit the same binding specificity, neutralization, and *in vivo* activity profile for mouse TNFα as golimumab demonstrates against human TNFα.

An overview of the repeat-dose toxicity studies with golimumab in cynomolgus monkeys as well as the supportive study with the murine analogous molecule cV1q is given in Table 1.

Table 1   Overview of the repeat-dose toxicity studies

Study Number	Species / Number of animals	Dose Levels (mg/kg) / Rout of admin.	Duration of dosing (Recovery period)	Product	NOAEL
T-2002-001	Cynomolgus monkey / 8/sex/group	0; 25; 50 twice a week/ SC	3 or 6 months (3 months)	Golimumab derived from C524A cell line	systemic toxicity: 50 mg/kg
T-2000-007	Cynomolgus monkey / 5/sex/group	0; 10; 50 once a week/ IV	1 month (37 days)	Golimumab derived from C466D cell line	50 mg/kg
T-2004-006	Cynomolgus monkey / 8/sex/group	0; 10; 50 once a week/ IV	6 months (3 months)	Golimumab derived from C524A cell line	50 mg/kg
T-098-004	Mouse CD-1/ 30/sex/group	0; 10; 40 once a week/ IV	3 or 6 months (3 months)	Analogous mouse anti-TNFα monoclonal antibody cV1q	40 mg/kg

In cynomolgus monkeys, after 4-week intravenous administration of up to 50 mg/kg, no adverse effects were seen on the standard parameters studied. The NOAEL was set to 50 mg/kg. At NOAEL, the margin to maximum human exposure was approximately 600 (mean for male/female animals), based on C_{max} values.

In the 6-month subcutaneous study, using doses up to 50 mg/kg, no adverse effects due to golimumab treatment were seen on standard parameters. An increase (between 1.5 to 2 times control values) in total lymphocytes, T-lymphocytes, T-helper lymphocytes, T-cytotoxic/suppressor lymphocytes, and naïve T-lymphocytes was seen in both sexes and both treated groups. During the recovery period, no difference to controls was detected. Further, an increase in B-lymphocyte counts were seen and these changes remained during the recovery period. These results suggest a slight immunostimulatory effect; albeit without histopathological correlates. Several organ weights, including organs of the immune system, were increased or decreased. Effects on the immune system organs weights are expected and also a known effect from other TNFα blockers.

Despite the increase in total lymphocytes, it is agreed by the assessor that a NOAEL can be set to 50 mg/kg, which gives a margin to maximum human exposure of approximately 600 (mean for male/female animals), based on C_{max} values and 50 based on AUC values.

In the 6-month intravenous study, using doses up to 50 mg/kg, no adverse effects due to golimumab treatment were seen on standard parameters. As after subcutaneous administration a dose-dependent increase (between 1.5 to 2 times control values) in most monkeys in the number of lymphocyte parameters. Males were generally affected more often, earlier, and for a longer duration than females.

The NOAEL was set to 50 mg/kg which gives a margin to maximum human exposure of approximately 650 (mean for male/female animals), based on C_{max} values and 100 based on AUC values.

- Genotoxicity

Genotoxicity studies as outlined in ICH S2B (1997) have not been conducted for golimumab. The lack of mutagenicity studies is reflected in the SPC (5.3).

- Carcinogenicity

No carcinogenicity study was performed with golimumab as standard rodent studies are not meaningful due to lack of pharmacologic activity in this species. However, with the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

The lack of long-term carcinogenicity studies is reflected in the SPC and addressed in the risk management plan.

- Reproduction Toxicity

Reproductive toxicity was evaluated both in cynomolgus monkeys and in CD-1 mice, using the analogous mouse anti-TNFα antibody cV1q. An overview of these studies including noteworthy findings is given in Table 2. Although the relevance of the findings for humans is unknown, information about the results of the fertility and general reproductive function study in mice using cV1q has been included in the SPC (5.3).

Table 2   Reproductive and developmental toxicity studies performed with golimumab and cV1q

Type of Study / Number	Species / Number of animals	Duration of dosing	Dose Levels (mg/kg) / Route of admin.	Product	Special feature	Noteworthy Findings	NOAEL
Embryo-foetal development/ T-2003-005	Cynomolgus monkey / 12 to 14/ group	GD20 to GD50	25; 50 twice weekly / SC	Golimumab derived from C524A cell line	Immuno-toxicity (cord blood)	-	50 mg/kg
Pre- postnatal development/ T-2004-007	Cynomolgus monkey / 12/group	GD50 to LD 33	25;50 twice weekly / SC	Golimumab derived from C524A cell line	Immuno-toxicity in neonates	-	50 mg/kg
Fertility/ T-098-003	Mouse CD-1/ 25/sex/group	M: 10 weeks[a] F: 3 weeks[b]	10; 40 once weekly / IV	cV1q*	-	M: increased precoïtal interval; decreased fertility rate F: moribund animals, lowered pregnancy rate	10 mg/kg
Embryo-foetal development/ T-096-011	Mouse CD-1/ 21/treated group	GD6 and GD12	10; 40 once weekly / IV	cV1q*	-	-	40 mg/kg
Pre- postnatal development/ T-2001-002	Mouse CD-1/ 25/group	GD6 to LD15	10;40 once weekly / IV	cV1q*	Immuno-toxicity	F0: moribund animals F1 F: significant decrease in gestation body weight	10 mg/kg
combined embryofoetal development /.pre- postnatal development/ T-2003-013	Mouse CD-1/ 9 to 15/group	GD6 to GD18 or GD6 to LD15	40 once weekly / IV	cV1q*	milk and serum analysis and immunology analysis.	F1: significant decrease in viability	40 mg/kg

[a]8-weeks prior to cohabitation and continuing for 2 weeks after cohabitation, [b]2-weeks prior to cohabitation and on GD 0 and 7
*Analogous mouse anti-TNFα monoclonal antibody

GD = Gestation Day, LD = lactation day, F = Female, M = Male,

Fertility and early embryonic development
Male and female fertility was studied in mice. After intravenous injections once weekly, with doses up to 40 mg/kg, no effect were seen on standard parameters. A slightly lower pregnancy rate, within historical control range, was seen; 92%, 91% and 76% for the 0, 10 and 40 mg/kg groups, respectively. Also, a decreased male fertility rate was seen; 92, 91 and 76 for the respective groups of mice. The clinical relevance of these findings, using the mouse homolog of golimumab, cV1q, is unknown.

Embryo-fetal development
In mice, dosed up to 40 mg/kg, no adverse effects were seen on standard maternal and fetal parameters. NOAEL for maternal and fetal parameters was 40 mg/kg. At 40 mg/kg, the exposure multiple to maximum clinical exposure was approximately 40 for dams and 20 for the fetuses, based on serum concentrations.

In cynomolgus monkeys, using doses up to 50 mg/kg during organogenesis, no treatment-related effects were seen on maternal and fetal standard parameters. NOAEL was set to 50 mg/kg, and at this dose the exposure multiple to maximum clinical exposure was approximately 400 for the dams during organogenisis, and 15 for the dams and 8 for the foetuses at the time of C-section, based on serum concentrations. When comparing AUC levels at 50 mg/kg, the exposure multiple to maximum clinical exposure was approximately 200 for the dams during organogenesis.

Prenatal and postnatal development, including maternal function
In cynomolgus monkeys, no adverse effects were seen related to golimumab treatment, including effects on the immunological development in the F1 infants followed for 6 months post delivery. NOAEL for the dams and the developing fetus and F1 infants was 50 mg/kg. At this dose the exposure multiple to maximum clinical exposure was approximately 370 for the dams after the last dose and 130 for the infants at 2 weeks of age, based on serum concentrations.

Golimumab was found in breast milk, however the concentrations were low (4 µg/mL in the 50 mg/kg treatment group) and were approximately 350-fold lower than maternal serum concentrations during the lactation period.

In mice, in one of the two pre-and postnatal development studies, a decreased humoral immune response, evaluated in the IgM antibody response to the T-cell dependent antigen, was statistical significant in F1 females when evaluated as total spleen cell activity. In the second study, no effect was seen in the IgM antibody-forming cell response to the T-dependent antigen, when evaluated at either 11 or 22 weeks of age, in F1 males and females exposed *in utero* or *in utero* and during lactation.

No studies in which the offspring (juvenile animals) are further dosed and/or further evaluated were submitted. In the prenatal and postnatal development study T-2004-007, where cynomolgus infants were exposed to golimumab *in utero* (from Day 50 of gestation) and during lactation (until Day 33 after delivery), golimumab was transferred across the placenta from mothers to foetuses and the offspring had high serum golimumab concentrations after birth. At two weeks of age (the first serum samples collected from the infants) the serum golimumab concentration in the neonates from the treated mothers was 537 µg/ml, which gives a margin to human exposure after intended clinical dosing of approximately 130. By 6 months of age the golimumab concentration was 3.2 µg/ml.

- Toxicokinetic data

From the toxicokinetic data collected as part of the toxicity studies it can be concluded that the animals in the toxicity studies have been extensively exposed to golimumab or, when the studies were performed in mice, to cV1q. The margins to human exposure, when comparing C_{max} and AUC values are in general large, from 50 and above, however it has to be taken into account that golimumab was shown to have 34-fold less affinity and to be 72-fold less potent in neutralizing cynomolgus TNFα

compared to affinity and neutralization of human TNFα. Therefore, even though the monkeys have been extensively exposed to golimumab, the "true" margins to human exposure are difficult to assess. However, since the clinical safety profile of an anti-TNFα agent is fairly well established, the uncertainty of the exposure margins relative to the human exposure is not considered a concern.

- Local tolerance

The local tolerance of golimumab was evaluated in a single dose subcutaneous injection study and in a 3-week and a 4-week twice-weekly subcutaneous injection study in cynomolgus monkeys, with doses up to 10 and 50 mg/kg. In these studies, mild skin irritation and inflammation at the injection sites were seen as a result of injection of a foreign protein. Even though the formulation used in these studies was not the one intended for commercialization, the excipients in finished product cause no concern.

- Other toxicity studies

Tissue cross-reactivity study:
The cross-reactivity of biotinylated golimumab with normal human tissues has been evaluated in a GLP-compliant *in vitro* study using cryosections of normal, adult human tissue specimens (T-2000-004). The antibody concentrations used in the definitive study were 10 μg/ml and 1 μg/ml. Golimumab did not stain the majority of the normal human tissue sections evaluated. There was slight to moderate staining of the adnexal epithelium of the skin from 2 of 3 donors and slight staining of the keratinocytes in the epidermis (stratum malpighi) of nipple skin overlying the breast (mammary gland) from 1 of 3 donors. The staining was observed at 10 μg/ml but not at 1 μg/ml.

Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) was submitted. The Applicant justified the lack of an ERA by referring to EMEA/CHMP/SWP/4447/00 which states that proteins are exempted since they are unlikely to result in any significant risk to the environment. This was considered acceptable.

2.4   Clinical aspects

Introduction

The applicant has undertaken one Phase 2b dose-finding study and a total of five multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical studies - three in RA, and one in PsA and AS, respectively. An overview of the main clinical studies is presented in Table 3.

Golimumab to be used in clinical trials has been produced by two different cell lines, C466D and C524A. In the early Phase 1 and Phase 2 studies lyophilized formulations were used; all Phase 3 studies used a liquid formulation supplied in glass vials (LIV).

Table 3   Overview of the main clinical studies with golimumab

Study ID	Study Posology (every 4 weeks; SC)	Subjs by arm entered	Duration	Diagnosis Incl. criteria	Primary Endpoint
Rheumatoid arthritis					
C0524T05 GO-BEFORE	0, 50, 100 mg	Pbo+MTX: 160 100mg: 159 50mg+MTX:159 100mg+MTX:159	Blinded, Pbo-controlled W 0-52	Active RA and MTX naive	ACR 50 W24
C0524T11 GO-AFTER	0, 50, 100 mg	Pbo:140 50mg: 140 100mg:140	Pbo-controlled W 0-24 Unblinded active treatment W24-52.	Active RA and previous treatment with anti-TNFα	ACR 20 W14

Study ID	Study Posology (every 4 weeks; SC)	Subjs by arm entered	Duration	Diagnosis Incl. criteria	Primary Endpoint
				agent(s)	
C0524T06 GO-FORWARD	0, 50, 100 mg	Pbo+MTX: 120 100mg: 120 50mg+MTX: 80 100mg+MTX: 80	Pbo-controlled W 0-24. Blinded active treatment W24-52.	Active RA despite MTX therapy	ACR 20 W14
Psoriatic arthrits					
C0524T08 GO-REVEAL	0, 50, 100 mg	Pbo: 113 50 mg: 146 100 mg 146	Pbo-controlled: W 0-24; Blinded active treatment W24-52.	active PsA despite current / previous DMARD or NSAID therapy, no previous anti-TNFα	ACR 20 W14
Ankylosing spondylitis					
C0524T09 GO-RAISE	0, 50, 100 mg	pbo = 78 50 mg = 138 100 mg = 140	Pbo-controlled: W 0-24; Blinded active treatment W24-52.	active AS despite current / previous DMARD or NSAID therapy, no previous anti-TNFα	ASAS 20 W14.

DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal anti-inflammatory drug; ACR: American College of Rheumatology*; ASAS: Ankylosing Spondylitis assessment score

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetic characteristics of golimumab have been investigated in several clinical studies in patients with RA, PsA and AS as well as in healthy volunteers. The studies investigated both i.v. and s.c. administration of golimumab and included intensive as well as sparse sampling schemes. An overview of these studies is presented in Table 4.

Table 4   Summary of clinical studies with pharmacokinetic information

Study ID	Phase	Dose Regimen[a]	Route of Administration[b]	Number of Subjects Randomized	Sampling Scheme[c]
Rheumatoid Arthritis					
C0466T01	1	0.1, 0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg SD	IV	36	Intensive
C0466T02	1	0.3, 0.6, 1.0, and 3.0 mg/kg SD; 0.3 and 1.0 mg/kg q2 weeks x 3	SC	53	Intensive
C0524T02	2	50, 100 mg q2 weeks or q4 weeks	SC	172	Sparse
C0524T05	3	50, 100 mg, q4 weeks	SC	637	Sparse
C0524T06	3	50, 100 mg, q4 weeks	SC	444	Sparse
C0524T11	3	50, 100 mg, q4 weeks	SC	461	Sparse

Study ID	Phase	Dose Regimen[a]	Route of Administration[b]	Number of Subjects Randomized	Sampling Scheme[c]
Psoriatic Arthritis					
C0524T08	3	50, 100 mg, q4 weeks	SC	405	Sparse
Ankylosing Spondylitis					
C0524T09	3	50, 100 mg, q4 weeks	SC	356	Sparse
Healthy Subjects					
C0524T13	1	100 mg SD	SC	30[e]	Intensive
C0524T23	1	50, 100 mg SD	SC	51	Intensive
C0524T24	1	100 mg SD	SC	156	Intensive
C0524T15	1	100 mg SD	SC or IV	78	Intensive

a SD = single dose, q2 weeks = every 2 weeks, q4 weeks = every 4 weeks

b SC = subcutaneous, IV = intravenous

c Intensive sampling schemes enable determination of the full PK profile using a non-model approach (e.g., non-compartmental analysis). Sparse sampling schemes require a model-based approach to characterize the full PK profiles

e. C0524T13 was not a randomized study, and 30 subjects were assigned to a single treatment group in the study

In the majority of studies, serum concentrations of golimumab were determined using a so called sandwich electrochemiluminescence immunoassay (sandwich ECLIA). The method has in general been well described and sufficiently validated. As commonly observed for these types of methods, the occurrence of antibodies against golimumab interfered with the detection of golimumab, i.e. the antibody titres are underestimated when antibodies are present. The lower limit of quantification (LLOQ) of this assay was 200 ng/ml with an MRD (minimum required dilution) of 10, however, it should be noted that this limit is not low enough to estimate trough concentrations in all subjects following the administration of 50 mg every 4 weeks (q4w).

An enzyme immunoassay (EIA) was used for detection of antibodies against golimumab. This method measures only the non-complexed antibodies and thus, complexes already formed between golimumab and the antibody are not detected by this method. Furthermore, occurrence of golimumab in the serum samples interferes with the method and results in false negative results. Accordingly, it is difficult to identify individuals with a positive immune response and the practical usefulness of the present enzyme immunoassay method is low, as the majority of the samples are classified as inconclusive and the impact of being antibody positive on efficacy and safety is difficult to evaluate. Only in one clinical study (C0524T02) the presence of anti-golimumab neutralizing antibodies was determined. A functional cell-based bioassay was applied for samples identified as immune response positive by the EIA.

Pharmacokinetic parameters were calculated by non-compartmental techniques for studies with intensive sampling schemes. In addition, three population PK evaluations were performed, describing pharmacokinetics in RA, PsA and AS patients, respectively, by using the pharmacokinetic information derived from sparse sampling in four of the performed Phase 3 studies. These data were analysed by non-linear mixed effects modelling using NONMEM version 6 employing the first order conditional estimation method with interaction (FOCE-I).

Descriptive and summary statistics have been used. The generally accepted methods for bioequivalence assessment were used.

- Absorption

The **systemic exposure** has been studied following single and repeated s.c. injections every 2 or 4 week in patients with RA, PsA, and AS. In addition, a few single dose s.c. studies were performed in healthy volunteers and single dose i.v. administration was given to healthy volunteers and RA patients. Three population pharmacokinetic analyses were performed on the basis of data from RA patients

(studies C0524T05 and C0524T06), PsA patients (study C0524T08) and AS patients (study C0524T09), respectively.

The **absolute bioavailability** following a 100 mg s.c. injection in the upper arm, abdomen and thigh was similar and on average 51%. Following an s.c. injection the serum concentration profile of golimumab rises slowly and exhibits several peaks (reasons unknown) and maximum serum concentrations of golimumab occur during the first week after administration in most patients. The systemic exposure of a s.c. injection delivered with needle and syringe or with a prefilled syringe/auto-injector resulted in comparable systemic exposure.

The variability in systemic exposure is substantial; coefficient of variations across studies varied over 25-59% for C_{max} and over 47-59% for AUC. The coefficient of variation in trough serum golimumab samples in study C0524T02 (RA patients) ranged from 72% to 110%. The extent of intra-individual variability in trough serum golimumab concentrations in the same study was roughly estimated to approximately 20-30% 20% and is thus not a main contributor to the overall variability. Differences in body weight, immune response and concomitant methotrexate can only explain a minor part of the observed variability. The residual variability estimated in the population PK analyses was relative large (28% CV).

- Distribution & Elimination

Golimumab has a limited tissue distribution and a low clearance with estimated values (mean +/- standard deviation) of volume of distribution and clearance being 6.9±2.0 ml/day/kg and 115±19 ml/kg, respectively. The **mean terminal half-life** ranged from 11 to 14 days following single s.c. doses (50 to 300 mg) and the half-life for a typical patient weighing 70 kg derived from the population analyses ranged from 10-13 days in the three disease populations applied for, i.e. RA, PsA and AS. The elimination pathways have not been described; however, as a human IgG1κ monoclonal antibody, golimumab is presumably metabolised in the same manner as any other endogenous IgG, i.e degraded into small peptides and amino acids via catabolic pathways.

- Dose proportionality and time dependencies

The pharmacokinetics appear to be roughly dose proportional following single s.c. injections over a dose range of 50 to 100 mg and following repeated s.c. injections (every second or forth week) over a dose range of 50 to 100 mg.
Steady-state is on average achieved at week 12, being in accordance with a half-life of approximately 2 weeks. However, median serum trough concentrations obtained over longer time periods (up to 52 weeks) indicate a tendency toward a decrease over time, which may be related to increased formation of antibodies toward golimumab and possibly an increased risk of inefficacy. A positive immune response was estimated in the **population PK** model to increase CL/F of golimumab by 75-190%. As the LLOQ of the detection assay was not low enough to estimate trough concentrations in all subjects the observed median values may be upward biased.

- Special populations

The main part of the pharmacokinetic studies was performed in patients and three **population PK analyses** were performed separately for each of the applied for indication.

No studies have been performed in patients with **impaired renal or hepatic organ function**, which is acceptable for this type of drug. The lack of data in patients with renal or hepatic impairment is reflected in the SPC.

From a clinical efficacy perspective a correlation between efficacy and body weight was indicated as there was a trend that subjects with high body weight, i.e. >100 kg, have lower ACR responses rates, and this is reflected in the SPC. No substantial effect of **age**, i.e. elderly, was identified in the pharmacokinetic population analysis.

- Pharmacokinetic interaction studies

No formal *in vivo* drug interaction studies have been performed. On the basis of observed golimumab concentrations and the population pharmacokinetic analysis (following 50 and 100 mg golimumab every fourth week) it was identified that serum concentrations of golimumab are increased by concomitant MTX treatment. The magnitude of the effect varied between studies, but the effect is not considered to be of such an extent that dose adjustments are required. The reason for the interaction is unknown but has been observed for previous TNFα-inhibitors. The population pharmacokinetic modelling does not indicate a large effect of NSAIDS, corticosteroids and sulfasalazine on the PK of golimumab. Increased cytokine levels during inflammation have been observed to reduce the activity of cytochrome P-450 enzymes. Thus, upon treatment with golimumab the cytokine levels are reduced and thereby the activity of cytochrome P-450 enzymes may become normalised (increased) and may indirectly affect the plasma concentrations of drugs metabolised by these enzymes. However, at present the clinical relevance of these findings is unclear.

- Pharmacokinetics using human biomaterials

PK studies using human biomaterials such as *in vitro* permeability studies and protein binding studies, as traditionally performed for small molecules, were not considered applicable or useful since golimumab is a human monoclonal antibody intended for subcutaneous administration.

Pharmacodynamics

No separate pharmacodynamic studies were conducted in healthy subjects. The effects of golimumab on biomarkers of inflammation and bone and cartilage metabolism were explored in the Phase 3 studies, as well as anaemia and cardiovascular markers.

- Mechanism of action

TNFα is a cytokine with multiple biologic actions, including protection against bacterial, fungal, parasitic, and viral infections, modulation of cell growth, mediation of inflammatory responses and interaction in a network with other lymphokines to modulate cells involved in immune response. TNFα has been implicated in autoimmune and inflammatory diseases such as RA, PsA, and AS, as well as psoriasis, ulcerative colitis, and Crohn's disease. There is support from non-clinical studies that golimumab is a selective TNFα inhibitor.

- Primary and Secondary pharmacology

Primary pharmacology

Across all the Phase 3 studies, treatment with golimumab alone or in combination with MTX resulted in significant reductions in levels of selected inflammatory markers including IL-6, TNFα, ICAM-1, VEGF and matrix metalloproteinase-3 (MMP-3) compared with control. Treatment with golimumab alone or in combination also resulted in significant decreases in rheumatoid factor (RF) levels and improvement in CRP levels.

In the studies C0524T06, C0524T08 and C0524T09, golimumab alone or in combination with MTX resulted in significant changes in levels of select markers of bone metabolism (increases in osteocalcin and procollagen type I N-terminal propeptide (PINP) and decreases in deoxypyridinoline (DPD) levels) compared with treatment with the control group.

Secondary pharmacology

Anaemia and Cardiovascular Markers
Anaemia is a common complication in patients with RA. The effect of golimumab on anaemia of inflammation was explored in the Phase 3 studies by assessing changes in haemoglobin levels and anaemia biomarkers in subjects with anaemia at baseline. Although relatively few subjects had

anaemia at baseline in this program, golimumab treatment increased haemoglobin levels in anaemic patients (C0524T06; C0524T11). However, general improvement of disease activity is often followed by normalised haemoglobin levels. For golimumab, no conclusion can be drawn due to the small number of patients. Furthermore, no clear trend was evident for the effect of golimumab on anaemia in the MTX-naïve RA, PsA or AS studies.

Exploratory evaluations of the effect of golimumab treatment on cardiovascular disease were included in two of the Phase 3 RA studies (C0524T05 and C0524T06). In both studies, greater improvements (reductions) were seen in cardiovascular inflammatory markers, including fibrinogen, IL-6, IL-8, and ICAM-1, in the golimumab + MTX groups than in the placebo + MTX groups whereas the effects of golimumab on lipid parameters were more mixed. However, these exploratory evaluations of cardiovascular markers do not allow any general conclusion of the effects of golimumab.

Clinical efficacy

Efficacy data up to Week 24 were submitted in the initial application, while all studies were ongoing with up to 5 years follow up planned for. During the review process, summaries of 52 weeks efficacy data for signs and symptoms from studies T05, T06 (RA) and T08 (PsA), as well as updated safety data were provided. In all Phase 3 studies, golimumab was administered as an s.c. injection, and subjects were given the option of self-administering the injection after appropriate training. Dosing was scheduled at 4-week (q4w; 28 day) intervals in these studies, but a 3 to 7 day dose window was specified in the protocol that included 30 to 31 days, which corresponds with monthly dosing.

- Dose response study

Rheumatoid arthritis
One Phase 2b dose finding study was undertaken in RA (C0524T02). The study was designed to evaluate the efficacy and safety of four dosing regimens of golimumab + MTX in patients with active RA despite MTX therapy and to determine the appropriate dose for phase 3 studies. The dosing regimen tested were 50 or 100 mg golimumab s.c. injections either every 2 (q2w) or every 4 weeks (q4w).

The primary endpoint, ACR20 response at Week 16, was met as a statistically significant effect was shown in the combined golimumab group. The 100 mg dose given q2w showed clear effects as well, while the 50 mg dose q4w was barely significantly better than placebo, and the other dose regimens were non-significant. Thus, there was no clear cut dose-response relationship demonstrated.

Although the 100 mg q2w dose regimen was the only treatment group with statistical significant results as compared to placebo group with regards to the primary endpoint, the regimen selected for Phase 3 were golimumab 50 mg q4w and 100 mg q4w. In general, the rationale for the dose selection for Phase 3 studies is not well justified.

Psoriatic arthritis and Ankylosing spondylitis
Doses for PsA and AS were selected based on the Phase 2b study in RA together with theoretical considerations. The lack of dose finding in these populations could be questioned, but it is also considered reasonable to choose the dose based on experience in RA. Thus, these dose recommendations are accepted. For both PsA and AS, use of golimumab as monotherapy was proposed. This proposal was acceptable as adequate data has been provided in its support (see description of Main studies below).

- Main studies

Rheumatoid Arthritis (RA)

The efficacy of golimumab in the treatment of adults with active RA was investigated in three Phase 3 trials, each trial evaluating a different subpopulation of subjects with moderate to severe disease. The

three RA populations studied represent the majority of patients encountered in clinical practice who are candidates for anti-TNF therapy, namely patients with active disease despite MTX therapy (C0524T06), Patients previously treated with an anti-TNF therapy (C0524T11) and patients naïve to MTX (C0524T05).

An overview of the key design elements of these Phase 3 studies is given in Table 5.

Table 5   Overview of key design elements of Phase 3 studies in RA through Week 24

Design Elements	C0524T06 GO-FORWARD	C0524T11 GO-AFTER	C0524T05 GO-BEFORE
Phase 3, multicenter, randomized	√	√	√
Placebo-controlled, double-blind	through Week 52 (subjects randomized to placebo + MTX crossed over at Week 24 in a blinded fashion to receive golimumab 50 mg + MTX)	through Week 24	through Week 52
Population (adults with active RA)	Active disease despite MTX therapy	active disease and previous treatment with anti-TNFα agent(s)	active disease and MTX-naïve
(Co)Primary Endpoint(s)	• ACR 20 response at Week 14 • improvement from baseline in HAQ at Week 24	• ACR 20 response at Week 14	• ACR 50 response at Week 24 • change from baseline in vdH-S score at Week 52
Subjects randomized Treatment group (n)	444 • PBO + MTX (133) • GLM 100 mg + PBO MTX (133) • GLM 50 mg + MTX (89) • GLM 100 mg + MTX (89)	461 • PBO (155) • GLM 50 mg (153) • GLM 100 mg (153)	637 • PBO + MTX (160) • GLM 100 mg + PBO MTX (159) • GLM 50 mg + MTX (159) • GLM 100 mg + MTX (159)

GLM = golimumab PBO = placebo

Subjects should have no evidence of active TB and no history of latent TB. Risk for tuberculosis (TB) was similarly evaluated in all individuals in all studies, and if needed, TB prophylaxis was given. Subjects with a history of, or concurrent, congestive heart failure (CHF), including medically controlled, asymptomatic CHF were excluded from all Phase 3 studies.

Summaries of the individual RA studies are presented below.

Study C0524T06 (GO-FORWARD)

This was a placebo-controlled study in subjects with active RA despite ongoing MTX.

METHODS

Study Participants

Adult subjects with a diagnosis of RA (American College of Rheumatology (ACR) criteria) for at least 3 month and active RA despite MTX therapy were included.

The study design excluded, amongst other criteria, subjects with other inflammatory diseases, those previously treated with anti-TNFα therapy and/or disease modifying anti-rheumatic drugs (DMARDs)/systemic immunosuppressives within 4 weeks prior to the first study as well as subjects who had a current serious infection or chronic or recurrent infectious diseases or certain other medical conditions.

Treatments

Details of the study treatment in each arm and the key time points during the study are depicted in Figure 1.
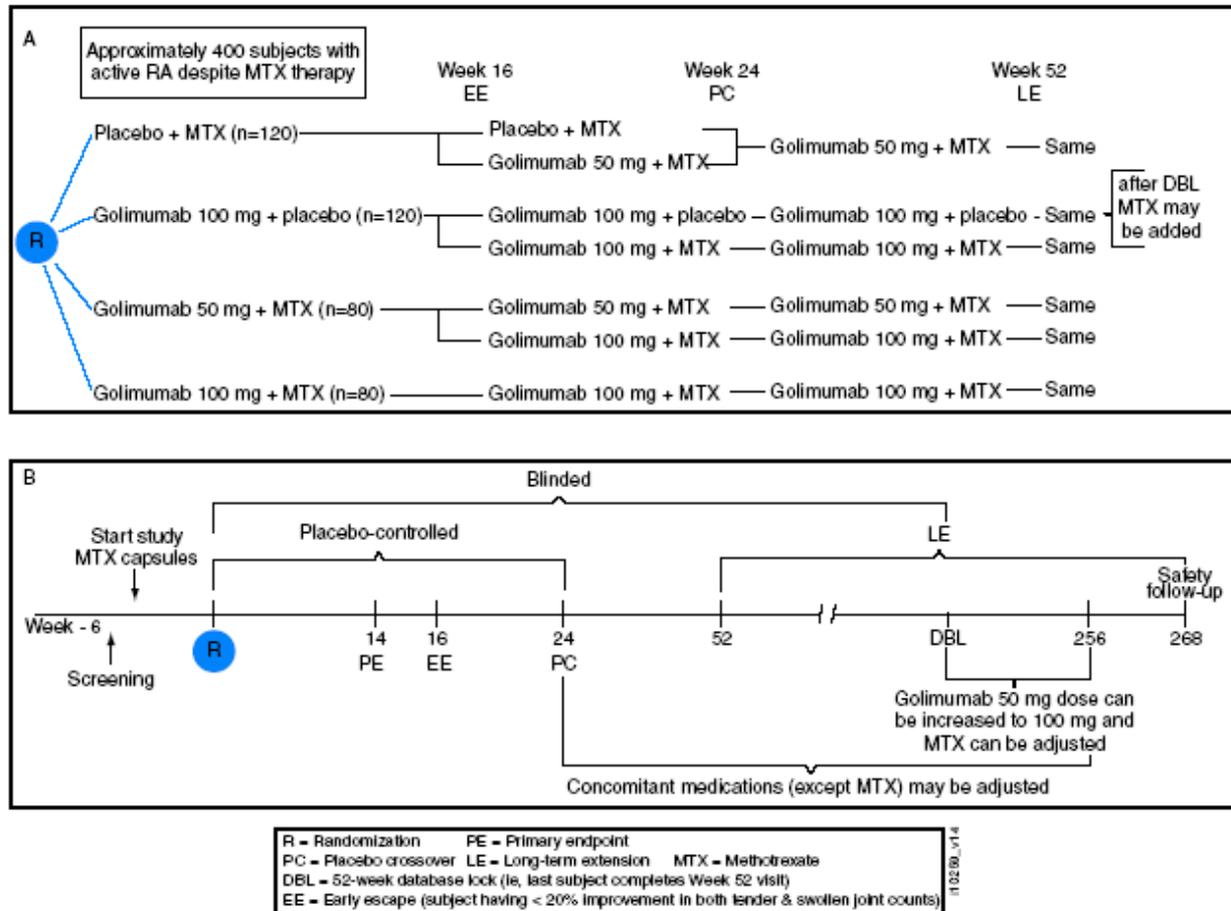

***Figure 1 Study schema (C0524T06). Panel A: Study treatment of each arm; Panel B: Key time points during the study.** (EE=early escape; DBL=database lock; LE=long-term extension; MTX=methotrexate; PC=placebo crossover; PE=primary endpoint; R=randomization)*

Objectives

The primary objective of this study was to assess the efficacy of golimumab in subjects with active RA despite MTX therapy.

The secondary objectives were to assess the safety of golimumab, the effects of golimumab on structural damage and health-related quality of life, and the population pharmacokinetics of golimumab.

Outcomes/endpoints

Two co-primary endpoints were used:
  1)   ACR 20 response at Week 14 <u>and</u>

2) Improvement from baseline in health assessment questionnaire (HAQ) at Week 24 (these were not provided in this application.)

The four major secondary endpoints of this study were:
- The change from baseline in van der Heijde Modified Sharp (vdH-S) score at Week 24
- The proportion of subjects with DAS28 (using CRP) response at Week 14
- The proportion of subjects with an ACR 20 response at Week 24
- The improvement from baseline in HAQ at Week 14

Signs and symptoms of RA:

- An American College of Rheumatology (ACR) 20/50/70 response was defined as a $\geq$ 20/50/70% improvement in Swollen joint count (66 joints) **and** tender joint count (68 joints) **and** $\geq$ 20/50/70% improvement in three of the following five assessments:
  1. Patient's assessment of pain (VAS)
  2. Patient's global assessment of disease activity (VAS)
  3. Evaluator's global assessment of disease activity (VAS)
  4. Patient's assessment of physical function as measured by the HAQ
  5. CRP

Functional status of the subject:

- The Health assessment questionnaire (HAQ) disability index is a 20 question instrument which assesses the degree of difficulty the subject had in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the previous week. Responses in each functional area are scored from 0 (no difficulty) to 3 (inability to perform a task in that functional area). The minimal clinically important difference is 0.22.

Sample size

The sample size was determined assuming an ACR20 response rate of at least 55% in patients treated with golimumab + MTX and 35% of patients treated with MTX alone. Based on this assumption, 120, 80, and 80 subjects in Groups I, III, and IV (MTX treatment groups) were required to achieve > 90% power. In addition, assuming that 55% of subjects receiving golimumab monotherapy (Group II) and 35% of subjects receiving MTX montherapy (Group I) achieve an ACR20 response, Group II will require 120 subjects to achieve > 85% power to detect significant difference between Group II and Group I using a chi-square test at α = 0.05 (2-sided).

This sample size will also provide > 90% power to detect a difference in improvement from baseline in HAQ between treatment groups using a 2-sided t-test on van der Waerden normal scores of improvement from baseline in HAQ at α = 0.05, assuming the mean improvement from baseline in HAQ as 0.21 for placebo, -0.47 for Group III, and -0.39 for Group IV.

Randomisation

A total of approximately 400 subjects were to be randomly assigned using IVRS in a 3:3:2:2 ratio to one of four treatment groups in a blinded fashion on Day 1. Randomization was to be stratified by investigational site.

Blinding (masking)

For the Week 24 data analysis presented, a select group of Centocor personnel who were not directly involved with the conduct of the study were unblinded. At each visit, the randomization center IVRS provided the responsible authorized health professional at the site with the proper kit number for each subject's study medication. Unblinding of the investigator was to be done only for compelling safety reasons.

Statistical methods

Descriptive statistics, such as the mean, median, standard deviation (SD), range, and the interquartile range for continuous variables, and counts and percentages for categorical variables were used to summarize most data. Pearson's chi-square test was used to compare binary categorical data.

The primary efficacy and selected secondary efficacy analyses were based on all subjects who were randomized at Week 0, i.e. the intent-to-treat (ITT) population. In the analyses of primary efficacy endpoints, the first test compared golimumab at any dose + MTX (golimumab 50 mg + MTX and 100 mg + MTX combined) versus placebo + MTX, if the result was significant, then pair wise comparisons of golimumab 50 mg + MTX versus placebo + MTX and golimumab 100 mg + MTX versus placebo + MTX were made.

All statistical testing was 2-tailed at a significance level of 0.05.
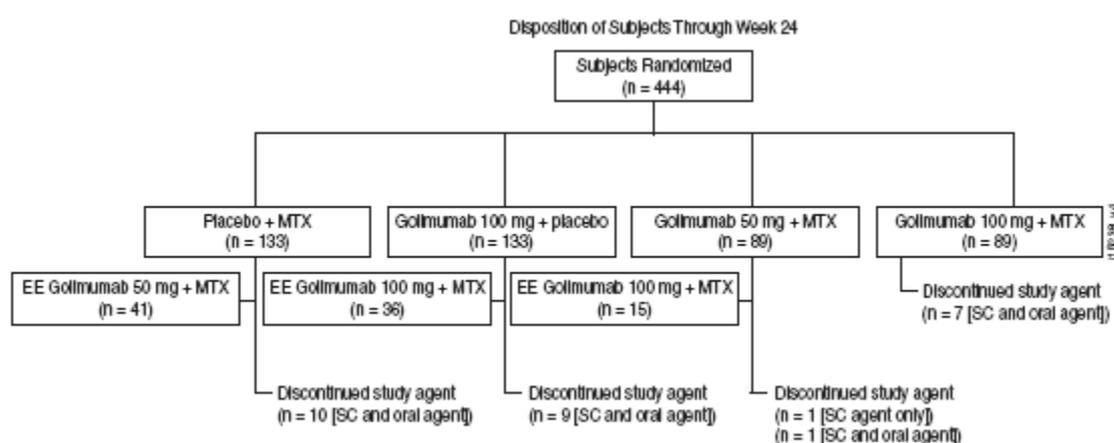
RESULTS

Participant flow

Figure 2 Disposition of subjects in study C0524T06 through Week 24.

Recruitment

The studied period up to 24 weeks was from December 2005 to September 2007.

Conduct of the study

Between October 2006 and February 2007 the applicant experienced significant issues associated with the availability of clinical trial supplies. All five Phase 3 studies were affected by these difficulties which led to disruptions in the study agent administration schedule for some subjects.

Baseline data

Demographic characteristics of subjects at baseline were generally similar across treatment groups with the majority of subjects being women (80.6%); 76.8% of subjects were Caucasian, 15.3% Asian; the median age was 51.0 years and median weight of 70.15 kg.

Baseline clinical disease characteristics were generally similar across treatment groups, and indicated the presence of long-standing disease. Among randomized subjects, median disease duration was lowest for the golimumab 50 mg + MTX group at 4.5 years and ranged up to 6.7 years in the golimumab 100 mg + MTX group.

Baseline values for the ACR core set of measurements indicated moderate to severe disease, and while generally balanced, suggested the possibility of relatively greater disease activity in the golimumab 50 mg + MTX group than in other treatment groups. Baseline disease characteristics of RA measurements other than the ACR core set were similar across all groups.

The distribution of co-morbidities was generally similar across all treatment groups as were the proportions of subjects at baseline using oral corticosteroids or NSAIDs specifically for RA.

Numbers analysed

All 444 subjects were analyzed for safety, efficacy, and health economics, and a subgroup of 158 subjects (150 planned) were analyzed for biomarkers.

Outcomes and estimation

In all treatment groups, except the golimumab 100 mg + MTX group, subjects meeting criteria for early escape (thus changing treatment as a result) had their last observation at or prior to Week 16 carried forward for Week 24 analyses. Subjects randomized to the golimumab 100 mg + MTX group and meeting the criteria for early escape did not change their treatment regimen, and as such, Week 24 observed values were used for analyses.

The results of the <u>two co-primary endpoints</u> were as follows:

Table 6   Results of co-primary endpoints; randomized subjects

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX		
			50 mg	100 mg	Combined
Subjects randomized	133	133	89	89	178
ACR 20 response at Week 14					
n	133	133	89	89	178
Subjects in response	44 (33.1%)	59 (44.4%)	49 (55.1%)	50 (56.2%)	99 (55.6%)
p-value		0.059	0.001	< 0.001	< 0.001
Improvement in HAQ at Week 24					
n	133	133	89	89	178
Mean ± SD	0.1316 ± 0.58374	0.2387 ± 0.66295	0.4663 ± 0.55255	0.4466 ± 0.51569	0.4565 ± 0.53302
Median	0.1250	0.1250	0.3750	0.5000	0.4375
IQ range	(-0.1250, 0.3750)	(-0.2500, 0.6250)	(0.1250, 0.7500)	(0.1250, 0.7500)	(0.1250, 0.7500)
Range	(-1.375, 2.125)	(-1.375, 2.375)	(-0.750, 2.125)	(-1.000, 1.625)	(-1.000, 2.125)
p-value		0.240	< 0.001	< 0.001	< 0.001

<u>Major secondary endpoints:</u>

For the secondary endpoints (ACR20 at 24 weeks, DAS28, HAQ), significance was reached for the combination therapies but not in the monotherapy group. For the more strict endpoints ACR50-90, significance was reached at week 24 for the 50 mg + MTX group at all levels but for 100 mg + MTX only for ACR50-70.

During the review process, the applicant submitted data on ACR, DAS28 and HAQ from Week 52. It should be noted that all subjects on placebo switched after Week 24, and a number of subjects in all groups had changed the original treatment regimen, during the study period. This makes interpretation of these results difficult. The Table below shows ACR results at Week 52, taking early escape and cross over into account.

Table 7   *ACR 20, ACR 50, ACR 70, and ACR 90 responses Week 52 by early escape or crossover status; randomized subjects (C0524T06)*

	Placebo + MTX →Goli 50 mg + MTX		Goli 100 mg + Placebo		Goli 50 mg + MTX		Golimumab 100 mg + MTX		
	Early Escape (Week 16-52)	Crossover (Week 24-52)[b]	100 mg Only[c]	100 mg → 100 mg + MTX[a]	50 mg + MTX Only[c]	50 mg + MTX → 100 mg + MTX[a]	100 mg + MTX Only[c]	100 mg + MTX → 100 mg + MTX[a]	Combined 100 mg + MTX
Subjects randomized	42	82	97	36	74	15	75	14	89
Week 52 (n)	39	81	87	31	70	15	65	14	79
ACR 20	23 (59.0%)	58 (71.6%)	60 (69.0%)	15 (48.4%)	58 (82.9%)	6 (40.0%)	45 (69.2%)	7 (50.0%)	52 (65.8%)
ACR 50	12 (30.8%)	37 (45.7%)	38 (43.7%)	7 (22.6%)	40 (57.1%)	2 (13.3%)	36 (55.4%)	4 (28.6%)	40 (50.6%)
ACR 70	7 (17.9%)	20 (24.7%)	23 (26.4%)	4 (12.9%)	22 (31.4%)	0 (0.0%)	29 (44.6%)	1 (7.1%)	30 (38.0%)
ACR 90	1 (2.6%)	4 (4.9%)	5 (5.7%)	0 (0.0%)	6 (8.6%)	0 (0.0%)	8 (12.3%)	0 (0.0%)	8 (10.1%)

Ancillary analyses

Sensitivity analysis

To test the robustness of the primary analysis, sensitivity analyses were performed to assess the following:

- The effect of considering subjects who discontinued s.c. study agent due to an AE prior to Week 14 as ACR 20 non responders at Week 14
- The effect of considering subjects with insufficient data to determine an ACR 20 response at Week 14 as ACR 20 non responders
- The effect of using observed data only to perform analysis for ACR 20 at Week 14
- The effect of missing 3 or more consecutive weekly oral doses on ACR 20 at Week 14
- The effect of observed data only on HAQ at Week 24

The sensitivity analyses confirm the robustness of the primary analysis.

Subgroup Analysis

The consistency of treatment effect for the primary endpoint was evaluated for multiple subgroups based on demographic features, geographic region, baseline disease characteristics, and baseline medications.
The results of these analyses were consistent with the primary analysis.

Study C0524T11 (GO-AFTER)
This was a placebo-controlled, 3-arm, parallel study in subjects with active RA previously treated with at least one anti-TNF therapy.

METHODS

Study Participants

Adult subjects with a diagnosis of RA for at least 3 months prior to screening and with active RA, defined as persistent disease activity with at least 4 swollen and 4 tender joints were included. Subjects must have been previously treated with at least 1 dose of a biologic anti-TNFα agent (i.e., etanercept, adalimumab, or infliximab) at least 12 weeks (infliximab) or 8 weeks (adalimumab or etanercept) prior to the first administration of study agent. Discontinuation of these medications could have been for reasons including, but not limited to, lack of efficacy, intolerance and/or inconvenience.

Subjects were allowed to be on background therapy, (alone or in combination) with MTX, sulfasalazine, hydroxychloroquine, oral corticosteroids, NSAIDs and analgesics.

The study design excluded, amongst other things, subjects with other inflammatory diseases, subjects who had had a serious adverse reaction to an anti-TNFα agent, or if they had received any investigational anti-TNFα agent or had received natalizumab, rituximab, or cytotoxic agents (chlorambucil, cyclophosphamide, nitrogen mustard) or other alkylating agents at any time. Furthermore, subjects who had a current serious infection or recurrent infectious diseases or a history of known demyelinating diseases or malignancy were excluded from trial participation.

Treatments

Details of the study treatment in each arm and the key time points during the study are depicted in Figure 3.
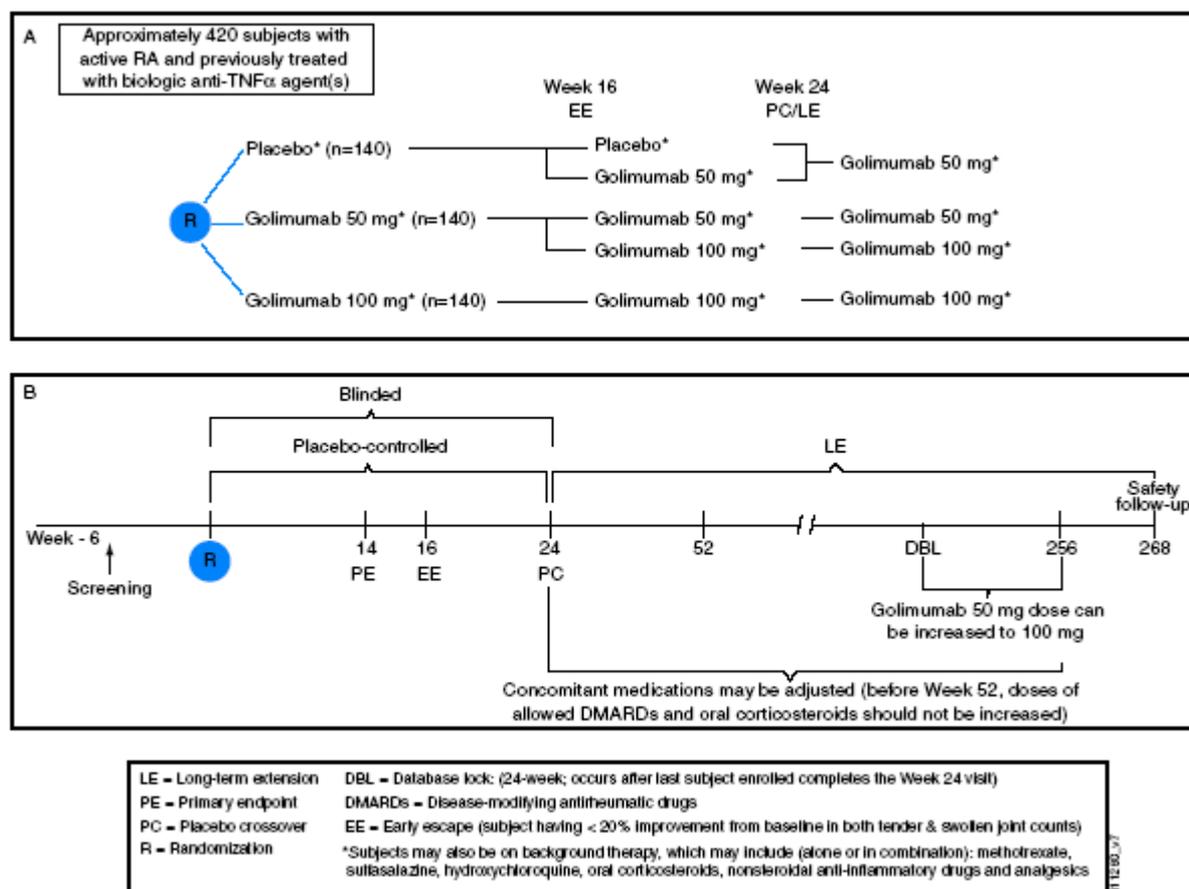

Figure 3 ***Study schema (C0524T11): Panel A shows study treatments; Panel B shows key timepoints during the study.*** *(EE=early escape; DBL=database lock; LE=long-term extension; MTX=methotrexate; PC=placebo crossover; PE=primary endpoint; R=randomization)*

Objectives

The primary objective of this study was to evaluate the efficacy of golimumab in subjects with active RA who had been previously treated with biologic anti-TNFα agent(s) by assessing the reduction in signs and symptoms of RA at Week 14.

The secondary objectives of this study were to assess the safety, physical function, pharmacodynamics, and population pharmacokinetics of golimumab in subjects with active RA who had been previously treated with biologic anti-TNF α agent(s).

Outcomes/endpoints

The primary endpoint of this study was the proportion of subjects with an ACR20 response at Week 14.

Major secondary analyses were ACR50 response at Week 14 ; DAS28 (using CRP) response at Week 14 ; ACR20 response at Week 24 and improvement from baseline in HAQ score at Week 24.

Sample size

This study was designed to evaluate if golimumab is superior to placebo in reducing signs and symptoms of RA (i.e., achieving an ACR 20 response at Week 14). The sample size of 140 subjects per treatment group will provide > 90% power assuming 50% of subjects use MTX at baseline (yes), and ACR 20 response in each treatment group is as given below:

Placebo | 30% in subjects with baseline MTX use (yes), 30% in subjects with baseline MTX use (no).
Golimumab 50 mg | 45% in subjects with baseline MTX use (yes), 40% in subjects with baseline MTX use (no).
Golimumab 100 mg | 55% in subjects with baseline MTX use (yes), 50% in subjects with baseline MTX use (no).

Randomisation

Approximately 420 subjects (140 subjects in each group) were to be enrolled and randomly assigned in a 1:1:1 ratio to the different treatment groups. Randomization was stratified by investigational site and baseline MTX use (yes/no). Eligible subjects were randomly assigned using IVRS to receive a fixed s.c. dose of golimumab (50 or 100 mg) or placebo in a blinded fashion at Week 0 (Day 1).

Blinding (masking)

The study blind was to be maintained for all key individuals participating in this study until the 24-week data were locked. Study subjects and site personnel were blinded to treatment assignment. Unblinding of the investigator was to be done only for compelling safety reasons.

Statistical methods

All efficacy analyses were based on randomized subjects (i.e., the intent-to-treat population). The proportion of subjects with an ACR20 response at Week 14 following treatment with golimumab (golimumab 50 mg and golimumab 100 mg combined) was compared with the proportion of subjects with an ACR20 response at Week 14 following treatment with placebo using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by baseline MTX use (yes/no) at a 0.05 level of significance.
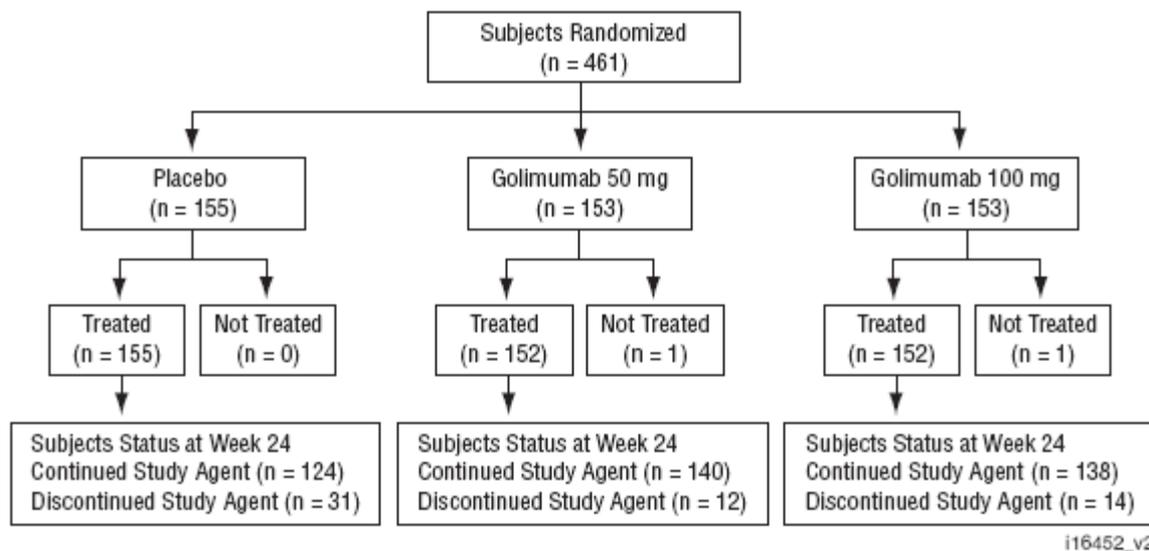
RESULTS

Participant flow

Figure 4 Disposition of subjects in study C0524T11 at Week 24.

More than twice as many subjects permanently discontinued study agent administration in the placebo group compared with the combined golimumab group (20.0% vs. 8.6%, respectively). Among all subjects, the most common reasons for discontinuing study agent administration were unsatisfactory therapeutic effect, AE, and other reasons (e.g., they withdrew consent or moved away from the study site).

Recruitment

The studied period up to 24 weeks was from February 2006 to September 2007.

Conduct of the study

The original protocol was amended twice to introduce changes with regard to eligibility, testing and prior treatment of patients with latent TB. For a description of clinical trial supplies issues see study C0524T06.

Baseline data

Demographic characteristics of subjects at baseline were generally similar across treatment groups. Approximately 80% of randomized subjects were women, 87.4% were Caucasian, 5.4% were black, and 1.7% were Asian. The median age was 54.0 years and the median weight was approximately 75 kg.

Clinical disease characteristics at baseline were generally similar across the randomized groups. The median duration of disease ranged from 8.65 years (golimumab100 mg) to 9.80 years (placebo). The majority of subjects were in functional Class II or III. The proportion of subjects receiving MTX at baseline was 66.8% for the combined golimumab group and 65.8% for the placebo group.

The placebo and individual golimumab groups were generally similar for all ACR core set of measurements except for HAQ and CRP, which were slightly worse in the placebo than in the combined golimumab group. These ACR core set of outcome measurements are indicative of subjects with moderately to severely active RA.

Medications and/or Therapies Prior to First Study Drug Administration:
The proportion of subjects who had taken prior medications for RA was similar across all treatment groups. Almost all subjects had received at least one DMARD and approximately half the subjects had received more than two DMARDs. Approximately 90% had received systemic corticosteroids. All subjects had received at least one anti-TNFα biologic for RA; 115 (24.9%) subjects had received two anti-TNFα biologics, and 43 (9.3%) had received three.

Across all randomized subjects, 58 % discontinued one or more prior anti-TNFα therapies due to lack of efficacy, 13% due to intolerance, and 29 % due to and/or reasons other than safety or efficacy (mostly for financial reasons).

Numbers analysed

All efficacy analyses were based on the intent-to-treat population, i.e. all 461 subjects randomized were analysed even though two were never treated.

Outcomes and estimations

- Primary endpoint

Table 8   Number of subjects who achieved an ACR20 response at Week 14 stratified by baseline MTX use; randomized subjects

| | Placebo | Golimumab | | |
		50 mg q4w	100 mg q4w	Combined
Subjects randomized	155	153	153	306
ACR 20				
n	155	153	153	306
Subjects in response	28 (18.1%)	54 (35.3%)	58 (37.9%)	112 (36.6%)
p-value		< 0.001	< 0.001	< 0.001
Subjects receiving MTX at baseline				
n	107	103	102	205
Subjects in response	18 (16.8%)	41 (39.8%)	42 (41.2%)	83 (40.5%)
Subjects not receiving MTX at baseline				
n	48	50	51	101
Subjects in response	10 (20.8%)	13 (26.0%)	16 (31.4%)	29 (28.7%)

Efficacy was observed in the golimumab groups irrespective of MTX use at baseline, although the proportion of subjects achieving ACR20 responses was greater in subjects who were receiving MTX at baseline.

- Major Secondary Endpoints

ACR 50 Response at Week 14
The proportion of subjects achieving an ACR 50 response at Week 14 was 18.3% in the combined golimumab group versus 6.5% in the placebo group (p < 0.001).
The proportions of subjects achieving an ACR 50 response at Week 14 in the individual golimumab groups were both superior to the placebo group with a slightly greater proportion of subjects in the golimumab 100 mg group than in the golimumab 50 mg group (50 mg 16.3%, p = 0.006 and 100 mg 20.3%, p < 0.001).

DAS28 (Using CRP) Response at Week 14
The proportion of subjects achieving a DAS28 (using CRP) response at Week 14 was 57.8% in the combined golimumab group versus 30.3% in the placebo group (p < 0.001). The proportions of subjects achieving a DAS28 (using CRP) response at Week 14 in the individual golimumab groups were both superior to the placebo group (50 mg 56.2%, p < 0.001 and 100 mg 59.5%, p < 0.001).

The proportion of subjects achieving an ACR20 response at Week 24

The proportion of subjects achieving an ACR 20 response at Week 24 was 38.9% in the combined golimumab group versus 16.8% in the placebo group (p < 0.001). The proportions of subjects achieving an ACR 20 response at Week 24 in the individual golimumab groups were both superior to the placebo group with a greater proportion of subjects in the golimumab 100 mg group than in the golimumab 50 mg group (50 mg 34.0%, p < 0.001 and 100 mg 43.8%, p < 0.001).

Change From Baseline in HAQ Score at Week 24

Clinically meaningful and significant improvement from baseline in the HAQ score at Week 24 was observed in the combined golimumab group versus the placebo group (median improvement of 0.2500 vs. 0.0000, respectively; p < 0.001).

Ancillary analyses

Sensitivity analyses demonstrated the robustness of these findings with respect to treatment failure and missing data rules.

Subgroup analyses were performed to evaluate consistency of the primary endpoint, the proportion of subjects with an ACR 20 response at Week 14, over demographic, baseline disease and clinical characteristics, and baseline and prior therapies for RA. A consistent treatment benefit versus placebo for subjects in the combined golimumab group was observed in all subgroups for demographic characteristics, with the exception of the subgroup of Black race.

A consistent treatment benefit versus placebo for subjects in the combined golimumab group was observed in a majority of subgroups in this category, with the exception of some subgroups (i.e., RA duration >1 to ≤ 3 years, number of swollen and number of tender joints ≤ 5, and functional Class I) in which lower efficacy were shown.

Study C0524T05 (GO-BEFORE)

This was a placebo-controlled study in subjects with active RA naïve to MTX.

METHODS

Study Participants

Adult subjects were eligible to participate in this study if they had a diagnosis of RA for at least 3 months before the first administration of study agent, were MTX-naïve and biologic anti-TNFα therapy-naïve, and had active RA. Subjects must not have received disease modifying anti-rheumatic drugs (DMARDs)/systemic immunosuppressives; intra-articular, IM, or IV corticosteroids; or anakinra within 4 weeks prior to the first study dose.

Definition of active RA and exclusion criteria were the same as in study C0524T06.

Treatments

Details of the study treatment in each arm and the key time points during the study are depicted in Figure 5.
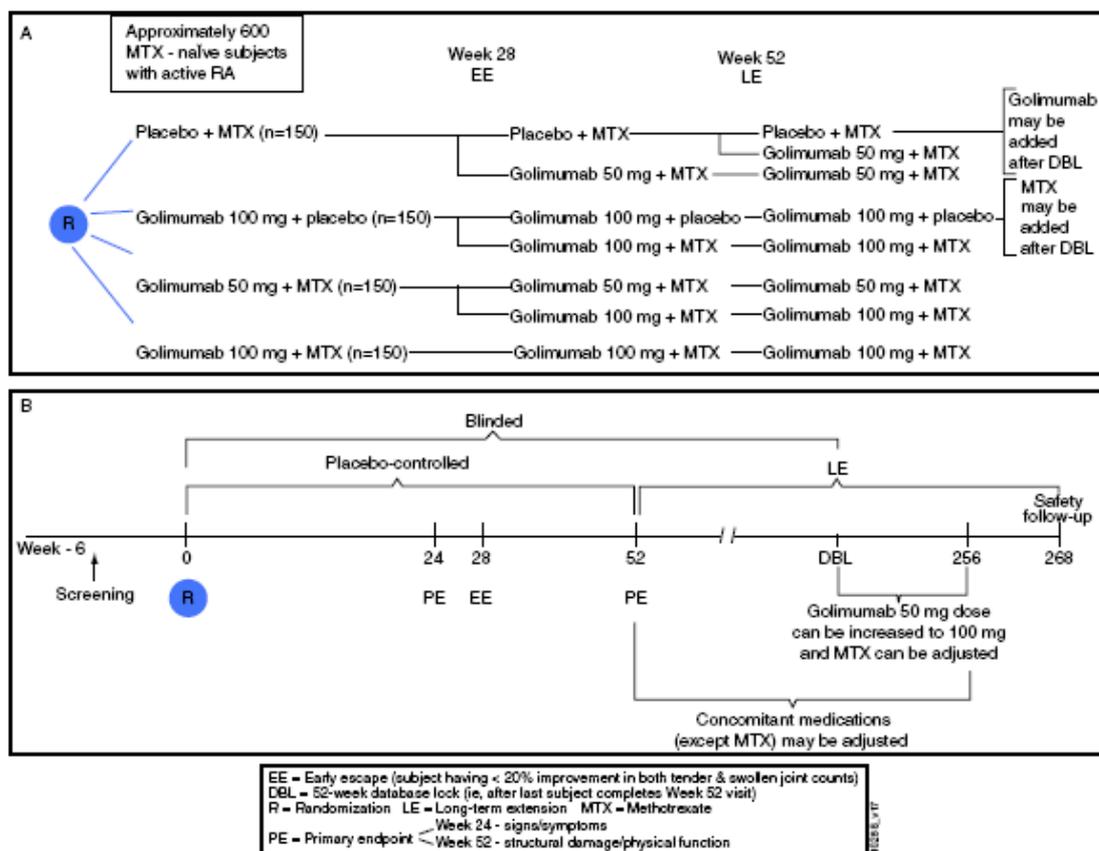
Figure 5 **Study schema (C0524T05): Panel A shows study treatments; Panel B shows key timepoints during the study.** *(EE=early escape; DBL=database lock; LE=long-term extension; MTX=methotrexate; PC=placebo crossover; PE=primary endpoint; R=randomization)*

Objectives

The primary objective of this study was to assess the efficacy of golimumab in subjects with active RA who have not been previously treated with MTX as measured by the reduction of the signs and symptoms at Week 24 and inhibition of progression of structural damage at Week 52.

The secondary objectives were to assess the safety of golimumab, the effect of golimumab on physical function and health-related quality of life, the pharmacodynamics (PD), and population pharmacokinetics (PK) of golimumab in subjects with active RA who have not been previously treated with MTX.

Outcomes/endpoints

The two co-primary endpoints were:
1) The proportion of subjects achieving ACR50 response at Week 24
2) Change from baseline in van der Heijde Modified Sharp score (vdH-S) at Week 52 to evaluate inhibition of progression of structural damage (to be reported after all subjects have completed 52 weeks of treatment and imaging, i.e. was not included in this submission).

The following major secondary analyses were performed:
1) The proportion of subjects achieving an ACR20 response at Week 24.
2) The proportion of subjects with abnormal CRP at baseline achieving an ACR50 response at Week 24.

For further details on the main endpoints see description of study C0524T06.

Sample size

The sample size of 150 subjects per treatment group was calculated to provide > 98% power to detect a difference in ACR50 response between treatment groups using the 2-sided CMH test at α=0.050. This sample size also provided approximately 85% power to claim non-inferiority of golimumab 100 mg + placebo compared with placebo + MTX at α=0.050 using a one-sided equivalence test assuming the proportion of golimumab 100 mg + placebo treated subjects with ACR50 response is not less than 0.10 compared with proportion of subjects with ACR50 response in the placebo + MTX treated group.

Randomisation

Approximately 600 subjects, stratified by screening CRP level (< 1.5 mg/dL; ≥ 1.5 mg/dL) and investigational site, were randomly assigned in a 1:1:1:1 ratio to 1 of the 4 treatment groups via a centralized IVRS at Week 0.

Blinding (masking)

The study blind was to be maintained for all key individuals participating in this study until the 24-week data were locked. Study subjects and site personnel were blinded to treatment assignment. Unblinding of the investigator was to be done only for compelling safety reasons.

Statistical methods

The primary efficacy and selected secondary efficacy analyses were based on all subjects who were randomized at Week 0, i.e. intent-to-treat (ITT) population. The Cochran-Mantel-Haenszel (CMH) test or chi-square test was to be used as appropriate to compare the proportion of subjects responding to treatment. All statistical tests were 2-sided and performed at α=0.050. Continuous response parameters were to be compared using an analysis of variance on the van der Waerden normal scores.

RESULTS

Participant flow

A total of 637 subjects were randomized.
Figure Figure 6 below shows the disposition of randomized subjects through Week 24.
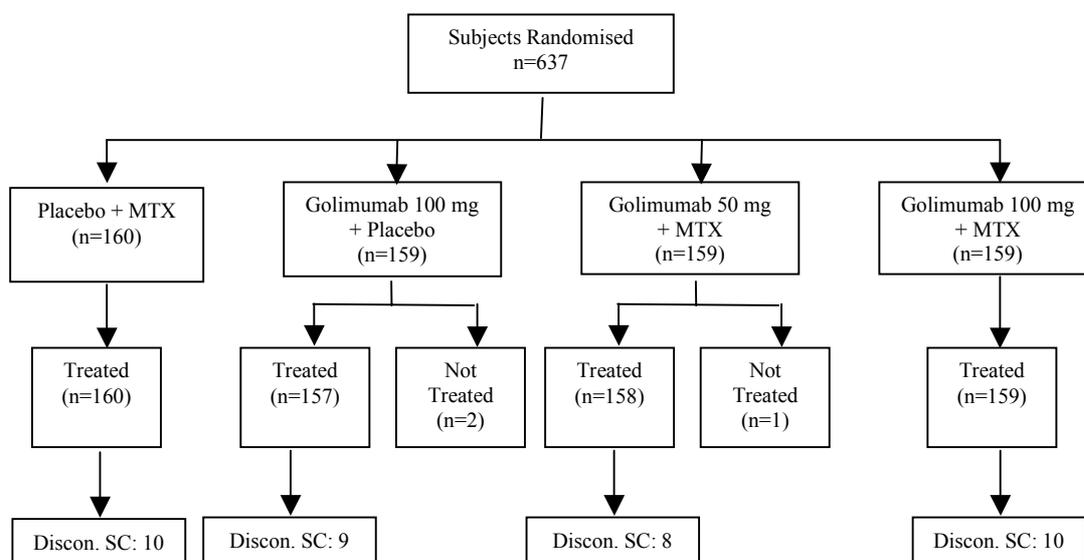

Figure 6   Disposition of subjects in study C0524T05 through Week 24.
        Discon. SC = Discontinuation of subcutaneous study agent.

Through Week 24, discontinuation of s.c. study agent occurred in 5.8% of randomized subjects and discontinuation of oral study agent occurred in 6.4% of randomized subjects. The main reason for discontinuation was due to AE, in particular in the MTX + golimumab combination group. There was no discontinuation due to lack of efficacy in the combination group, but 3 in the golimumab monotherapy group. In the MTX monotherapy group, only one stopped treatment due to lack of efficacy. The proportion of subjects who discontinued s.c. or oral study agent was different because a subject could discontinue oral study agent but continue s.c. study agent.

Recruitment

The studied period up to 24 weeks was from December 2005 to October 2007.

Conduct of the study

The original protocol was amended three times. Changes incorporated in these amendments that impact the data analyses through Week 24 included clarifications of the planned non-inferiority analysis, the addition of analyses to evaluate improvement in tender and swollen joints and clarifications regarding the interim clinical pharmacology analysis. For a description of clinical trial supplies issues see study C0524T06.

Baseline data

Demographic characteristics at baseline were generally well balanced across treatment groups. Of all randomized subjects most were female (82.9% overall), Caucasian (72.4% overall, followed by Asian 18.4% overall); the median age was 50.0 years overall and the median weight was 69.0 kg overall.

Baseline disease characteristics indicated that subjects had moderate disease, with most subjects having relatively short duration of disease (median from 1.0 to 1.8 years). The mean number of swollen joints at baseline ranged from approximately 15 to 16 and the mean number of tender joints ranged from approximately 27 to 29. Treatment groups were generally well balanced with respect to baseline disease characteristics, with the exception that the duration of morning stiffness was longer in the placebo + MTX group (120 minutes) than in all other groups (105 minutes in the 50 mg + MTX group and 90 minutes in the 100 mg + placebo and in the 100 mg + MTX groups). In addition, in the golimumab 100 mg + MTX group, the 25th percentile for CRP level was lower (0.30 mg/dl) than that observed in all other groups (from 0.50 mg/dl to 0.55 mg/dl).

Numbers analysed

The primary efficacy and selected secondary efficacy analyses were based on all subjects who were randomized at Week 0 (ITT). As subjects were to be included in the efficacy analyses according to their assigned treatment group regardless of whether they received the assigned treatment, all 637 randomized patients were included in the analyses even though only 634 received treatment.

Outcomes and estimation

The results of the primary endpoint for which data were submitted were as follows:

1. ACR50 Response at Week 24

Table 9 ***Number of subjects who achieved an ACR50 response at Week 24 stratified by screening CRP level; randomized subjects***

| | Placebo + MTX | Golimumab 100 mg + Placebo | Golimumab + MTX | | |
			50 mg	100 mg	Combined
Subjects randomized ACR 50	160	159	159	159	318
n	160	159	159	159	318
Subjects in response	47 (29.4%)	52 (32.7%)	64 (40.3%)	58 (36.5%)	122 (38.4%)
p-value		0.521	0.042	0.177	0.053
Subjects with CRP <1.5 mg/dl at screening					
n	83	80	82	82	164
Subjects in response	21 (25.3%)	30 (37.5%)	33 (40.2%)	24 (29.3%)	57 (34.8%)
Subjects with CRP ≥1.5 mg/dl at screening					
n	77	79	77	77	154
Subjects in response	26 (33.8%)	22 (27.8%)	31 (40.3%)	34 (44.2%)	65 (42.2%)

A post-hoc (modified) mITT analysis of the primary endpoint was performed to assess the impact of including randomized subjects who did not receive treatment in the primary endpoint evaluation. When evaluating the proportion of subjects who achieved an ACR50 response at Week 24 in subjects who received at least one dose of s.c. or oral study agent, a comparison of the difference between the combined golimumab + MTX and placebo + MTX groups (38.5% vs 29.4%) resulted in a p-value of 0.049. Comparisons between all other groups were similar to that observed in the pre-specified ITT analysis, which included all randomized subjects.

Noninferiority testing between the golimumab 100 mg + placebo and placebo + MTX groups was planned as an analysis under the hierarchical approach for the primary endpoint. The lower bound of the 95% CI for the difference in ACR 50 response at Week 24 between these groups was -5.2% (noninferiority delta was –10%). These results suggest that the proportion of subjects who achieved an ACR 50 response was similar in the golimumab + placebo and placebo + MTX groups. A superiority test was performed, but superiority was not observed (p = 0.521).

Similar results were observed in the noninferiority analysis conducted using a 1-sided 97.5% CI, with the lower bound of the 97.5% CI for the difference in ACR 50 response at Week 24 between the golimumab 100 mg + placebo and placebo + MTX groups at -6.8% (noninferiority delta was –10%).

Major secondary endpoints:

For the endpoint ACR20, statistical significance was reached for the two combination groups but not for monotherapy. At week 24 the ACR responders at higher response levels were similar for all treated groups. Golimumab monotherapy was similar to MTX monotherapy. The combination therapy had slightly more responders but statistical significance was reached only for ACR90 in the 50 mg/MTX group.

During the review process, 52 weeks controlled data have been submitted. The intent-to-treat (ITT) analysis of ACR50 response performed at Week 24 for the primary endpoint was repeated at Week 52. Results from the ITT analyses for ACR20, ACR50, ACR70 and ACR90 are shown in Table 10.

Table 10   *Number of subjects who achieved an ACR20, ACR50, ACR70, and ACR90 response at Week 52; randomized subjects (C0524T05)*

	Placebo +MTX	Golimumab +100 mg Placebo	Golimumab + MTX + 50 mg	100 mg	Combined
Subjects randomised	160	159	159	159	318
ACR 20					
n	160	159	159	159	318
Subjects in response	83 (51.9%)	85 (53.5%)	95 (59.7%)	106 (66.7%)	201 (63.2%)
p-value		0.780	0.157	0.007	0.017
ACR 50					
n	160	159	159	159	318
Subjects in response	57 (35.6%)	61 (38.4%)	67 (42.1%)	77 (48.4%)	144 (45.3%)
p-value		0.609	0.235	0.021	0.044
ACR 70					
n	160	159	159	159	318
Subjects in response	35 (21.9%)	35 (22.0%)	45 (28.3%)	50 (31.4%)	95 (29.9%)
p-value		0.969	0.187	0.054	0.064
ACR 90					
n	160	159	159	159	318
Subjects in response	12 (7.5%)	7 (4.4%)	22 (13.8%)	19 (11.9%)	41 (12.9%)
p-value		0.242	0.068	0.181	0.077

Ancillary analyses

DAS28 Remission at Week 24

In the evaluation of DAS28 remission calculated using CRP at Week 24, a numerically greater proportion of subjects achieved DAS28 remission in the combined golimumab + MTX group than in the placebo + MTX group.

DAS28 Responders at Week 24

In the evaluation of DAS28 responders calculated using CRP at Week 24, there was a numerically greater proportion of DAS28 responders in the combined golimumab + MTX group than in the placebo + MTX group.

Psoriatic Arthritis

One study was undertaken in patients with psoriatic arthritis (PsA).

Study C0524T08 (GO-REVEAL)

METHODS

This was a multicenter, randomized, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab 50 mg or 100 mg administered as s.c. injections q4w in adult subjects with active PsA.

Study Participants

Subjects eligible for this study were men and women, 18 years of age or older, with a diagnosis of PsA for at least 6 months prior to first study agent administration who had active PsA despite current or previous disease-modifying antirheumatic drug (DMARD) or nonsteroidal anti-inflammatory drug (NSAID) therapy, and who had not previously been treated with anti-tumor necrosis factor (TNF) α therapy. Exclusion criteria included general contraindications for anti-TNF therapy and also for previous treatment with other anti-TNF/biologics. Furthermore, patients were not to have other inflammatory diseases, having received e.g. any systemic immunosuppressives or DMARDs other than MTX, or anakinra within 4 weeks prior to the first administration of study agent, or leflunomide,

alefacept or efalizumab within 3 months prior to the first administration of study agent. Previous use of any anti-TNFα, agent, or rituximab or natalizumab was not allowed.

Treatments

Details of the study treatment in each arm and the key time points during the study are depicted in Figure 7.
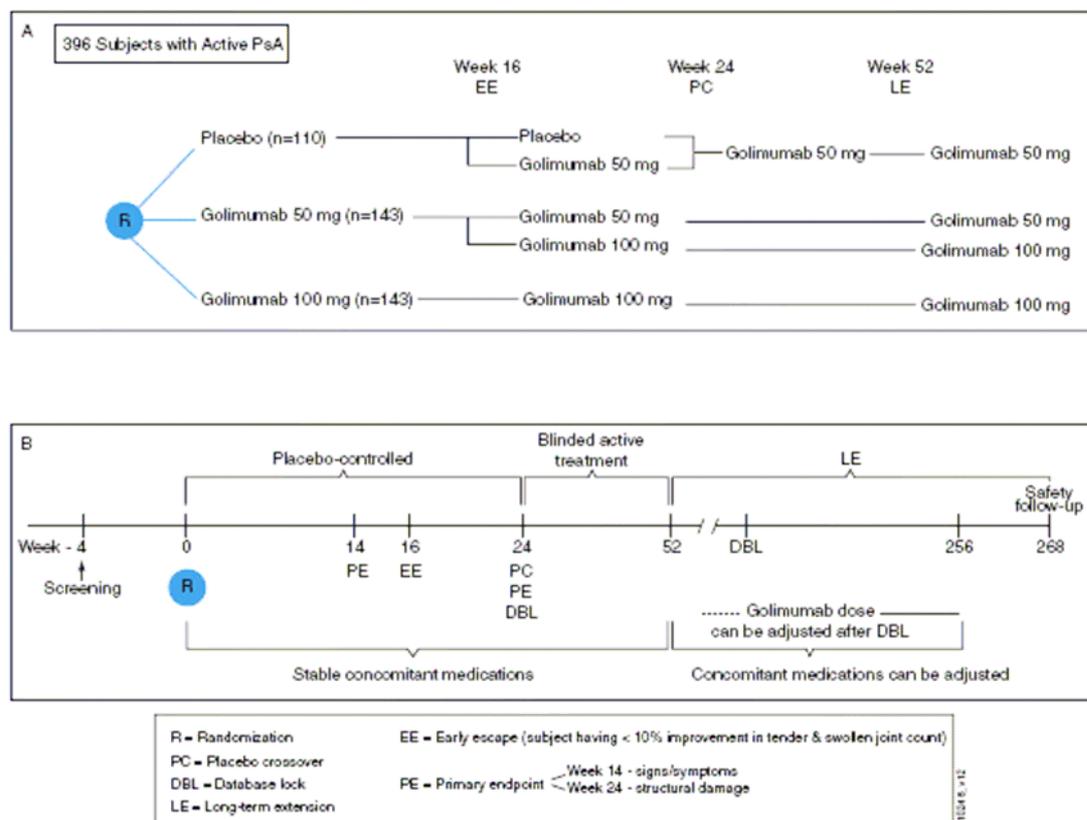

Figure 7   Study schema (C0524T08): Panel A shows study treatments; Panel B shows key timepoints during the study. (EE=early escape; DBL=database lock; LE=long-term extension; MTX=methotrexate; PC=placebo crossover; PE=primary endpoint; R=randomization)

Objectives

The primary objective of this trial was to evaluate the efficacy of s.c. injections of golimumab in subjects with active psoriatic arthritis (PsA) by assessing reduction in signs and symptoms of PsA and inhibition of progression of structural damage.

The major secondary objectives of this trial were to evaluate the efficacy of golimumab in:
- achieving sustained arthritis response,
- improving psoriatic skin lesions,
- improving physical function,
- improving quality of life; and to assess the safety of golimumab in subjects with active PsA.

Outcomes/endpoints

To test the primary objective, two co-primary endpoints have been established:
- ACR20 response at Week 14

- Change from baseline in PsA modified van der Heijde-Sharp (vdH-S) score at Week 24. Data for the co-primary endpoint of change from baseline in PsA modified van der Heijde-Sharp (vdH-S) score at Week 24 were not provided in this application.

Major secondary analyses included ACR20 response at Week 24 ; Psoriasis Area and Severity Index (PASI) 75 response at Week 14 ; 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.

In addition, other secondary endpoints related to the signs and symptoms of arthritis, psoriasis, physical function, and quality of life were evaluated (ACR50, 70 at Week 14 and 24, ACR-N index of improvement, PsARC response at week 14 and 24, DAS28 at Week 14 and 24).

Sample size

The study was powered to detect significant treatment differences in reducing signs and symptoms of arthritis and inhibition of progression of structural damage. With 396 subjects (110 placebo and 286 combined golimumab), a simulation of 5000 repetitions was used to calculate the power to detect a significant difference in the proportion of subjects achieving an ACR 20 response using a CMH test with stratification by subjects' baseline MTX usage (yes/no).

Randomisation

Subjects were randomly assigned to a treatment group via a centralized interactive voice response system IVRS at Week 0 (Day 1). Patients were stratified by investigational study site and baseline MTX use (yes/no).

Blinding (masking)

Randomization files containing treatment assignments for individual subjects were maintained in limited-access directories within the electronic data filing system at the central randomization center. Unblinding of the investigator was to be done only for compelling safety reasons.

Statistical methods

All efficacy analyses were based on randomized subjects; i.e., the intent-to-treat population (ITT). Pearson's chi-square test was used to compare binary categorical data, and the Cochran-Mantel-Haenszel (CMH) chi-square test to compare binary categorical data with stratification (stratified by baseline MTX usage [yes/no]). Analysis of variance (ANOVA) on van der Waerden normal scores with treatment and subject's baseline MTX usage as factors in the model was used to compare continuous data, unless otherwise specified. Additional analyses that adjusted for baseline differences were to be performed if baseline imbalances were found for any demographic factors. The two co-primary analyses were performed in a sequential manner.

RESULTS

Participant flow

Figure 8 below shows the subject distribution and disposition through Week 24 (randomized subjects).
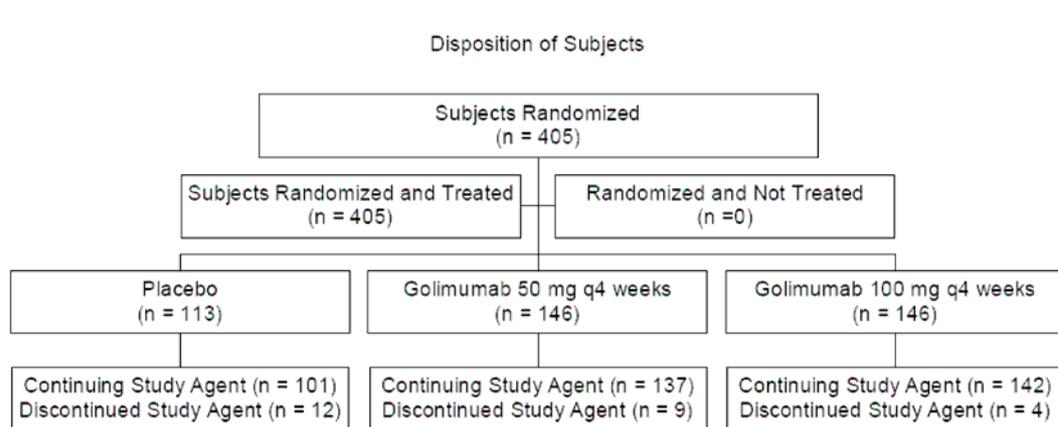
Figure 8 *Distribution and disposition of subjects in study C0524T08 through Week 24; randomized subjects.*

The AEs leading to discontinuation were in the placebo group 1 SAE of vertigo and headache, 1 SAE of urosepsis, 1 AEs of headache/nausea/chills, and 1 with an AE of isoniaside (INH)-induced hepatitis. With golimumab 50 mg, there was 1 SAE of acute abscess and 1 with elevated ALT/AST, and for golimumab 100 mg, 1 AEs with fatigue and 1 with prostate cancer.

Recruitment

The studied period up to 24 weeks was from December 2005 to May 2007.

Conduct of the study

For a description of clinical trial supplies issues see study C0524T06.

Baseline data

Demographic characteristics of subjects at baseline were generally well balanced across treatment groups with the majority of subjects being men (60.2%); most subjects were Caucasian (97.0%), the median age was 47.0 years and the median weight 84.0 kg.

Clinical disease characteristics at baseline, including duration of PsA and psoriasis, were generally similar across the randomized groups. Of note, the placebo group included a greater proportion of subjects with polyarticular arthritis with no rheumatoid nodules and a lower proportion of subjects with asymmetric peripheral arthritis than the combined golimumab group. Also, the majority of subjects (69.9% in the placebo and 74.3% in the combined golimumab groups) had ≥ 3% BSA involvement with psoriasis; the median BSA in these subjects was 8.0% (range 3, 62) in the placebo group and 10.0% (range 3, 99) in the combined golimumab group. And the median duration of psoriasis (17.50 years in the placebo group; 16.40 years in the combined golimumab group) was substantially greater than the median duration of PsA (5.10 years in the placebo group; 5.15 years in the combined golimumab group).

Baseline clinical characteristics of PsA from the ACR core set of outcome measurements were indicative of subjects with PsA of moderate to severe activity and similar across the treatment groups. The median numbers of swollen or tender joints were similar (range 9.5 to 11.0 and 18.0 to 19.0, respectively) across the treatment groups, and indicative of moderate to severe disease activity. Median CRP levels were the same (0.60 mg/dl) across all treatment groups (range 0.3, 12.1). The population had impaired physical function as indicated by mean ± SD HAQ scores of 1.027 ± 0.548 for the placebo group and 1.016 ± 0.636 for the combined golimumab group. Median VAS assessments, including patient's assessment of pain and both the patient's and physician's global assessments of disease activity were similar across treatment groups and indicative of moderate to severe disease activity.

Numbers analysed

The primary analyses at Week 16 were undertaken in 113 placebo patients, and 146 patients in each group of 50 or 100 mg golimumab.

Outcomes and estimation

- Primary endpoint

Table 11   Number of subjects who achieved an ACR20 response at Week 14 stratified by baseline MTX use; randomized subjects

| | Placebo | Golimumab | | |
		50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
ACR 20				
n	113	146	146	292
Subjects in response	10 (8.8%)	74 (50.7%)	66 (45.2%)	140 (47.9%)
p-value		< 0.001	< 0.001	< 0.001
Subjects receiving MTX at baseline				
n	55	71	71	142
Subjects in response	8 (14.5%)	38 (53.5%)	32 (45.1%)	70 (49.3%)
Subjects not receiving MTX at baseline				
n	58	75	75	150
Subjects in response	2 (3.4%)	36 (48.0%)	34 (45.3%)	70 (46.7%)

- Major secondary endpoints

ACR20 response at Week 24:
ACR20 response at Week 24 was achieved in a significantly greater proportion of subjects in the combined golimumab group (and in each golimumab dose group) than in the placebo group at Week 24 (56.5% vs. 12.4%; p < 0.001). ACR 20 response with golimumab treatment was noted as early as Week 4. At Week 24, 52.1% of subjects in the golimumab 50 mg group and 61.0% in the 100 mg group achieved an ACR 20 response.

PASI 75 Response at Week 14:
The proportion of subjects with ≥ 3% BSA psoriasis skin involvement at baseline who achieved a PASI 75 response at Week 14 was significantly greater (p < 0.001) in the combined golimumab group (49.3%) and in each of the individual golimumab groups than in the placebo group (2.5%). A larger proportion of subjects achieved a PASI 75 response at Week 14 in the golimumab 100 mg group (58.3%) than in the 50 mg group (40.4%).

Improvement from baseline in HAQ score at Week 24:
The improvement from baseline in the HAQ score at Week 24 was significantly greater (p < 0.001) in the combined golimumab group and in each of the individual golimumab groups than in the placebo group.

Change From Baseline in Physical Component Summary Score of the SF-36 at Week 14:
The change from baseline in SF-36 PCS scores at Week 14 was significantly greater (p < 0.001) in the combined golimumab group and in each of the individual golimumab groups than in the placebo group.

- Other efficacy endpoints

During the procedure, the applicant submitted Week 52 data. It should be noted that all subjects on placebo switched to active treatment after Week 24, and a number of subjects in all groups had changed the original treatment regimen during the study period. This makes interpretation of these

results difficult. The Table below shows ACR results through Week 52, taking early escape and cross over into account.

Table 12   ACR20, ACR50, and ACR70 responses after Week 24 through Week 52 by early escape or crossover status; randomized subjects (C0524T08)

	Placebo → Golimumab 50 mg		Golimumab 50 mg		Golimumab 100 mg		
	EE (Week 16-52)[a]	Crossover (Week 24-52)[b]	Goli 50 mg Only[c]	EE (50 mg → 100 mg)[a]	100 mg Only[c]	100 mg → 100 mg[a]	Combined 100 mg
Subjects randomized	51	51	118	28	121	25	146
Week 52							
N	47	49	102	26	115	20	135
ACR20	28 (59.6%)	43 (87.8%)	80 (78.4%)	11 (42.3%)	93 (80.9%)	7 (35.0%)	100 (74.1%)
ACR50	18 (38.3%)	22 (44.9%)	58 (56.9%)	7 (26.9%)	68 (59.1%)	3 (15.0%)	71 (52.6%)
ACR70	7 (14.9%)	13 (26.5%)	44 (43.1%)	3 (11.5%)	41 (35.7%)	1 (5.0%)	42 (31.1%)

a   Subjects in these groups met the early escape criteria at Week 16.
b   Subjects in this group did not discontinue study agent prior to Week 24 and crossed over at Week 24.
c   Subjects in these groups did not meet the early escape criteria at Week 16.

Ancillary analyses

- Sensitivity analysis

The sensitivity analyses undertaken supported the result of the primary analysis. The number of ACR20 responders was statistically significantly increased in both golimumab groups also at week 24 and differences were observed at the first evaluation time of 4 weeks. Also for the stricter ACR endpoints (ACR50 and ACR70), golimumab resulted in significantly more responders at week 14 and 24, which further supports clinically relevant efficacy. Furthermore, golimumab treatment resulted in statistically significant improvement of physical function at week 14 and week 24.

- Subgroups analysis

All subgroup analyses of ACR20 response at Week 14 across baseline demographics, disease characteristics, and disease severity demonstrated significant treatment benefit for golimumab over placebo. Selected subgroup analyses by gender, age, and baseline weight, MTX use, and CRP levels were performed for golimumab 50 mg and 100 mg and confirmed the efficacy of both doses across these baseline characteristics. Similar efficacy results for golimumab 50 mg and 100 mg were seen across all the quartiles of baseline weight, including the heaviest subjects.

Subgroup analyses indicate that in the most common PsA subgroup, the polyarticular form, golimumab is effective, as well as in the asymmetric form. Other PsA forms were uncommon, and thus no conclusion on effects in those groups can be drawn.

<u>*Ankylosing Spondylitis*</u>

Study C0524T09 (GO-RAISE)

Study C0524T09 is a multicenter, randomized, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab 50 mg or 100 mg administered as subcutaneous injections every 4 weeks in adult subjects with active AS.

<u>METHODS</u>

Study Participants

Men and women 18 years of age or older were eligible to participate if, for at least 3 months prior to the first administration of study agent, they had a diagnosis of definite AS, as defined by the 1984 Modified New York Criteria.

Furthermore, both the radiographic criterion and at least 1 clinical criterion must be met:
- Radiographic criterion: Sacroiliitis Grade ≥ 2 bilaterally or sacroiliitis Grade 3 to 4 unilaterally.
- Clinical criteria (at least 1):
  1. Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest
  2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes
  3. Limitation of chest expansion relative to normal values corrected for age and sex

Exclusion criteria included general contraindications for anti-TNF therapy and also for previous treatment with other anti-TNF/biologics. In addition, patients were not to have other inflammatory diseases, or complete ankylosis of the spine, or having received, e.g. any systemic immunosuppressives, or DMARDs other than MTX, SSZ, HCG within 4 weeks prior to the first administration of study agent, or leflunomide, alefacept or efalizumab within 3 months prior to the first administration of study agent. Previous use of any anti-TNFα, agent, or rituximab or natalizumab was not allowed.

Treatments

Details of the study treatment in each arm and the key time points during the study are depicted in Figure 9.
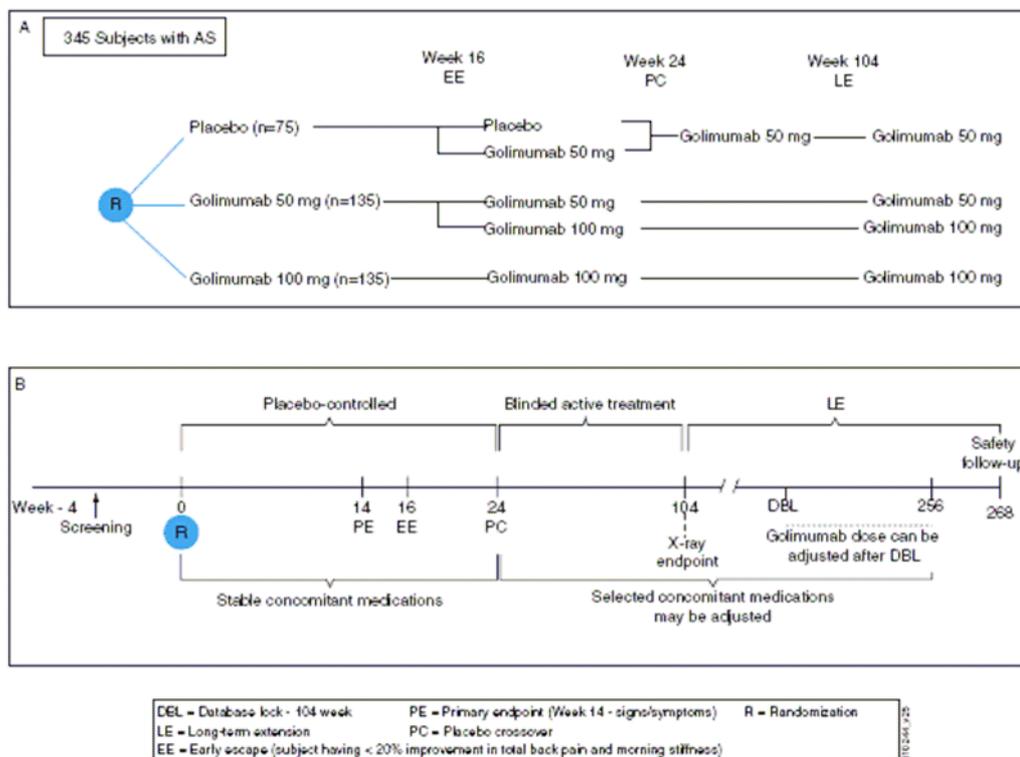

Figure 9 ***Study schema (C0524T09): Panel A shows study treatments; Panel B shows key timepoints during the study.*** *(EE=early escape; DBL=database lock; LE=long-term extension; MTX=methotrexate; PC=placebo crossover; PE=primary endpoint; R=randomization)*

Objectives

The primary objective of this trial was to assess the efficacy of s.c. injections of golimumab in subjects

with active AS as measured by reduction in signs and symptoms of active AS at Week 14.

The secondary objectives were to assess the overall safety of golimumab; the effects of golimumab on physical function, structural damage, and quality of life, and population PK and PD effects of golimumab.

Outcomes/endpoints

The primary endpoint is whether a subject achieved Assessment in Ankylosing Spondylitis (ASAS) 20 at Week 14.

The following major secondary analyses were performed in order of importance as specified below:
- The proportion of subjects achieving an ASAS 20 at Week 24.
- The change from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14.
- The change from baseline in the Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14.

Sample size

The sample sizes were chosen in order to obtain at least 300 subjects with 6 months exposure to golimumab, including placebo subjects who switch over to golimumab. It was assumed that half the subjects would have baseline CRP ≤ 1.5 mg/dl and half will have baseline CRP > 1.5 mg/dl and that there are 75 subjects in the placebo group and 135 subjects in each of the golimumab groups, a sample size which would be sufficient to attain at least 80% power.

Randomisation

Subjects were randomly assigned to a group via a centralized interactive active voice response system (IVRS) at Week 0 (Day 1). To ensure relatively even treatment balance within site, within screening CRP level (≤ 1.5 mg/dl; > 1.5 mg/dl), and within the study overall, subject allocation to a group was performed using an adaptive stratified randomization design (minimization with biased-coin assignment).

Blinding (masking)

Randomization files containing treatment assignments for individual subjects were maintained in limited-access directories within the electronic data filing system at the central randomization center. Unblinding of the investigator was to be done only for compelling safety reasons.

Statistical methods

All efficacy analyses were based on randomized subjects, i.e. the ITT. Pearson's chi-square test was used to compare binary categorical data, and Cochran-Mantel-Haenszel (CMH) chi-square test was used to compare binary categorical data with stratification (stratified by screening CRP level).

In the analyses of efficacy endpoints, the first test compared golimumab at any dose (golimumab 50 mg and 100 mg combined) versus placebo. If the results were significant, then pairwise comparisons of golimumab 50 mg versus placebo and golimumab 100 mg versus placebo were made. This method protected the significance level at 0.05: A golimumab dose group that was nominally significantly better than the placebo group would not be reported as significant unless the combined golimumab groups were significantly better than the placebo group as well.

All statistical testing was 2-tailed, at a significance level of 0.05.

Participant flow

Disposition of Subjects
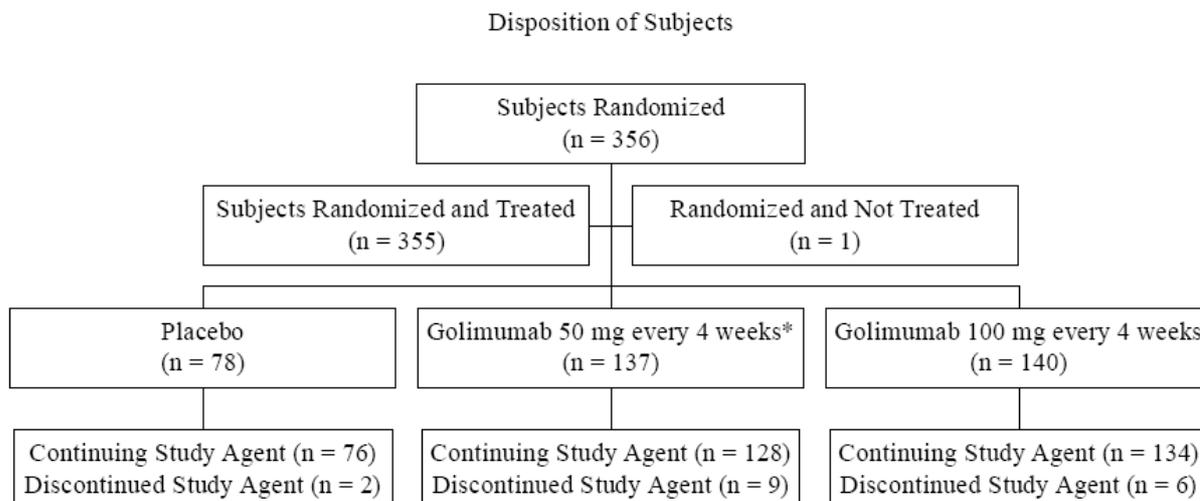
* 1 subject in golimumab 50 mg group was randomized but not treated.

Figure 10   Subject distribution and disposition through Week 24; randomized subjects.

Through Week 24, 17 (4.8%) subjects permanently discontinued study treatment, 5.4% in the combined golimumab group and 2.6% in the placebo group. The most common reasons were AEs and "other" (including withdrawal of consent).

Recruitment

The studied period up to 24 weeks was from December 2005 to May 2007.

Conduct of the study

For a description of clinical trial supplies issues see study C0524T06.

Baseline data

Demographic characteristics of subjects at baseline were generally well balanced across groups. The majority of the subjects were male (71.6%), consistent with the expected epidemiology of the disease. Most subjects were Caucasian (73.6%) or Asian (23.9%), the median age was 38.5 years (range: 18 to 83) and the median weight 75.2 kg (range: 35.0 to 142.6).

Baseline Disease Characteristics:
High proportions of subjects in the golimumab 50 mg (81.8%), golimumab 100 mg (84.3%), and placebo (84.6%) groups tested positive for human leukocyte antigen (HLA) B27. Approximately two thirds of the subjects had screening CRP ≤1.5 mg/dl with even distribution across treatment groups. Subjects had AS with a median duration of 5.15 years in the golimumab 50 mg group, 5.20 years in the golimumab 100 mg group, and 7.25 years in the placebo group. Since these differences may have affected response, duration of AS was added to a planned logistic regression analysis of ASAS 20 at Week 14.

Disease activity assessed by the subject on a 0 to 10 cm VAS included patient global assessment, total back pain and inflammation (morning stiffness). The median patient global assessment was 7.1 for the combined golimumab group and 7.2 for the placebo group. The median total back pain was 7.6 for both the combined golimumab and placebo groups. The median inflammation (morning stiffness) was

7.3 for the combined golimumab group and 7.05 for the placebo group. These levels of disease activity indicated the subjects experienced a moderately high level of pain and inflammation.

The median chest expansion was 3.5 cm, for both the combined golimumab and placebo groups, which is below normal as expected in AS patient population (6.5 cm for males, 4.5 cm for females, 35-44 years of age). Night back pain, also assessed by subjects on a 0 to 10 cm VAS, was 7.4 for both the combined golimumab and placebo groups.

The BASMI evaluation was slightly higher for the placebo group than the combined golimumab group. BASFI scores for all groups (placebo group: 4.93 and combined golimumab group: 5.25) indicated impaired physical function. Median Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 6.58 for the placebo group and 6.85 for the combined golimumab group indicate moderate to severe disease activity. The median value for the Jenkins sleep evaluation questionnaire were indicative of similar levels of impaired sleep across all treatment groups.

Numbers analysed

All efficacy analyses were based on the ITT population. See participant flow above for number of randomized subjects.

Outcomes and estimation

- Primary Endpoint

The proportion of subjects achieving ASAS 20 response at Week 14 in the golimumab 50 mg group (59.4%) and the golimumab 100 mg group (60.0%) was significantly greater ($p < 0.001$) than in the placebo group (21.8%) (Table 13).

Table 13   Number of subjects who achieved an ASAS 20 response at Week 14 stratified by screening CRP level; randomized subjects

| | Placebo | Golimumab | | |
		50 mg q4w	100 mg q4w	Combined
Subjects randomized	78	138	140	278
ASAS 20				
n	78	138	140	278
Subjects in response	17 (21.8%)	82 (59.4%)	84 (60.0%)	166 (59.7%)
p-value		< 0.001	< 0.001	< 0.001
CRP (mg/L)≤ 1.5 mg/dL				
n	46	79	81	160
Subjects in response	10 (21.7%)	40 (50.6%)	43 (53.1%)	83 (51.9%)
CRP > 1.5 mg/dL				
n	32	59	59	118
Subjects in response	7 (21.9%)	42 (71.2%)	41 (69.5%)	83 (70.3%)

Incorrectly entered CRP values resulted in 34 subjects being assigned to the wrong stratum at randomization. The misstratification did not impact the ASAS 20 analysis and therefore all other analyses were conducted with CRP levels as entered in the IVRS.

- Major secondary endpoints

For these analyses, each ASAS component value at Week 24 was replaced with the corresponding component value at Week 16 for subjects in the placebo and golimumab 50 mg groups who met early escape criteria at Week 16. No change was made for subjects in the golimumab 100 mg group since these subjects had no change in their dose per protocol.

ASAS 20 at Week 24:
The proportion of subjects achieving ASAS 20 response at Week 24 in the combined golimumab group (60.8%) was significantly greater ($p < 0.001$) than the proportion in the placebo group (23.1%).

The proportion of subjects achieving ASAS 20 response in each of the individual golimumab groups was also significantly greater (p < 0.001 for each) than the proportion in the placebo group. The proportion of subjects achieving ASAS 20 response at Week 14 was maintained through Week 24 for all groups.

BASFI at Week 14:
A median change from baseline of −1.42 was observed for the combined golimumab group and 0.095 for the placebo group. Both golimumab groups showed significant improvement (p < 0.001) over the placebo group. A negative/decreasing change from baseline is indicative of improvement in BASFI.

BASMI at Week 14:
No statistically significant differences were observed between golimumab groups and placebo group. A negative/decreasing change from baseline is indicative of improvement in BASMI.

- Other efficacy analysis

Significant treatment benefit for golimumab 50 mg and 100 mg groups was also seen using other measures of improvement in AS signs and symptoms. In particular, subjects in both golimumab groups had greater improvement than subjects in the placebo group as measured by the BASDAI, patient global assessment of disease activity, total back pain assessment, change in inflammation (measured by morning stiffness), change in CRP, and night back pain assessment at Weeks 14 and 24.

Ancillary analyses

- Sensitivity analyses

Five sensitivity analyses were conducted, including 3 planned and 2 post hoc analyses. In the planned analyses, subjects who discontinued due to AEs were considered nonresponders or subjects with insufficient data to determine ASAS 20 response were considered nonresponders or the analysis was based on observed data only. In the post hoc analyses subjects who missed at least 1 administration of study agent for any reason prior to Week 14 were considered nonresponders, or were excluded.

The proportion of subjects achieving ASAS 20 response in the combined golimumab group and in each of the individual golimumab groups in each sensitivity analysis remained significantly greater (p < 0.001 for each) than the proportion in the placebo group.

- Subgroup analyses

HLA-B27 status did not affect ASAS 20 response to golimumab.

The impact of weight on ASAS 20 response was not apparent in subjects receiving golimumab 100 mg dose. However, in the golimumab 50 mg treatment group, the ASAS 20 response was lower among subjects in the highest quartile of weight (> 87 kg). The odds ratios relative to placebo were not significant for golimumab 50 mg group in weight quartile > 87 kg and for golimumab 100 mg in weight quartile > 75.15 to ≤87 kg. An exploratory logistic regression analysis of the ASAS 20 response at Week 14 was run based on several factors including weight, and results indicated that with increasing weight, ASAS 20 response rate decreased.

In both sub groups of CRP levels, the ASAS 20 response in golimumab 50 mg and 100 mg groups was significantly greater (p < 0.001) than in the placebo group. Effects due to treatment group (p < 0.001), screening CRP (p = 0.0062), and weight (p = 0.0140) were significant.

- Relationship Between Antibodies to Golimumab and ASAS 20 Response

Samples for the measurement of antibodies to golimumab were collected at Weeks 0 and 24. In the golimumab 50 mg group, 3 (60.0%) of 5 subjects classified as positive, 7 (50.0%) of 14 classified as negative, and 67 (74.4%) of 90 classified as undetectable for antibodies to golimumab achieved an

ASAS 20 response. In the golimumab 100 mg group, 2 (66.7%) of 3 subjects classified as positive, 5 (50.0%) of 10 classified as negative, and 85 (68.0%) of 125 classified as undetectable for antibodies to golimumab achieved an ASAS 20 response.

None of the subjects positive for antibodies to golimumab was receiving MTX at baseline.

- Analysis performed across trials (pooled analyses and meta-analysis)

Effect of methotrexate
Across the 5 Phase 3 studies (C0524T05, C0524T06, C0524T08, C0524T09 and C0524T11), results show that golimumab + MTX results in higher mean steady-state trough golimumab concentrations ($C_{trough,\ ss}$) than treatment with the same golimumab dose without MTX in subjects from the 3 population of patients RA, PsA and SA.

Study Agent Self-administration
Of the 1537 treated subjects in the three RA studies, 234 (15.2%) subjects self-administered the study agent at least once through Week 24. Of the 17,617 injections administered through Week 24, 1195 (6.8%) were self-administered. No formal analyses were conducted in this subset of the study population.

- Clinical studies in special populations

Studies in special populations have not been conducted.

- Supportive studies

Antibody development
Overall the incidence of antibodies to golimumab was low, with a combined incidence of 4.3% across all subjects treated in Phase 3 and similar rates were shown in each rheumatologic indication. Across the 5 Phase 3 studies, the antibody incidence was similar for subjects receiving 50 mg + MTX (1.7%) compared with subjects receiving 100 mg + MTX (1.9%). Treatment with concomitant MTX resulted in a lower proportion of subjects with antibodies to golimumab than subjects receiving golimumab without MTX (approximately 2% versus 7%, respectively), although this was only evaluated in a randomized manner for subjects receiving golimumab 100 mg in C0524T05 and C0524T06. Approximately half of the antibody responses observed in the Phase 2 RA study were neutralizing as measured by a cell-based functional assay.

Limited safety data suggest that the presence of antibodies to golimumab may increase the risk of injection site reactions, which is reflected in the SPC. The small number of subjects positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and PK, clinical efficacy, or safety (injection site reactions) measures.

Clinical safety

The safety data are based on completed and ongoing clinical studies of golimumab in the three rheumatologic indications RA, PsA and AS. The five pivotal Phase 3 studies are being conducted for 5 years with safety data ranging from 24 weeks to over 52 weeks of treatment. The applicant has also considered safety data from other indications (e.g. severe, persistent asthma). Moreover, data in healthy subjects who were administered golimumab were presented.

The safety data for all three indications will be presented under the respective subheading below and/or as an integrated analysis across the combined indications, as most relevant. It should be pointed out that Week 16 was the primary focus for the safety comparisons, because this time point allows comparisons between the treatment groups that are unbiased by the extent of follow-up and extent of exposure. Data beyond Week 16 represent shorter follow-up for the placebo group compared with the

golimumab groups. In addition, the average follow-up at the last safety cut-off for golimumab 50 mg was shorter than for golimumab 100 mg. These facts lead to limitations of the safety data base for golimumab.

- Patient exposure

Table 14 shows the number of subjects for each indication through the latest safety data cut-off (June 2008) by length of exposure to subcutaneous golimumab (50 and 100 mg). For all 5 pivotal studies, there was a possibility of Early Escape (EE) at Week 16 or 28 depending on the study. The numbers of patients exposed for different lengths of time are sufficient to meet ICH recommendations.

Table 14   Number of subjects for each indication by dose and length of exposure to subcutaneous study agent; treated subjects in Phase 3 studies of RA, PsA, AS

| | RA | | | PsA | | | AS | | |
| | | Golimumab | | | Golimumab | | | Golimumab | |
	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg
Treated subjects in Phase 3 studies	449	772	896	113	248	225	77	213	165
Length of exposure (weeks)									
< 16	53 (11.8%)	64 (8.3%)	59 (6.6%)	19 (16.8%)	12 (4.8%)	31 (13.8%)	7 (9.1%)	12 (5.6%)	6 (3.6%)
16 to < 24	134 (29.8%)	94 (12.2%)	50 (5.6%)	56 (49.6%)	31 (12.5%)	26 (11.6%)	42 (54.5%)	26 (12.2%)	4 (2.4%)
24 to < 52	171 (38.1%)	211 (27.3%)	152 (17.0%)	38 (33.6%)	11 (4.4%)	7 (3.1%)	28 (36.4%)	7 (3.3%)	11 (6.7%)
≥ 52	91 (20.3%)	403 (52.2%)	635 (70.9%)	0 (0.0%)	194 (78.2%)	161 (71.6%)	0 (0.0%)	168 (78.9%)	144 (87.3%)
≥ 104	3 (0.7%)	29 (3.8%)	66 (7.4%)	0 (0.0%)	32 (12.9%)	51 (22.7%)	0 (0.0%)	25 (11.7%)	35 (21.2%)

- Adverse events

Concerning data presented through Week 24, the applicant explained that safety analyses included all randomized subjects who received at least 1 administration of study agent, and were summarized by actual treatment received. Subjects may appear in more than one column, because the AEs for subjects who changed treatment (i.e., from placebo to golimumab 50 mg or from golimumab 50 mg to golimumab 100 mg) are captured in two columns depending on whether the AE occurred before or after the change in treatment. Of note, due to escapee included in this study design, the data displays through Week 24 should be interpreted taking into consideration that there is a difference in the number of s.c. study agent administrations and the duration of follow-up for the placebo, golimumab 50 mg, and golimumab 100 mg groups and for subjects who entered treatment in EE. In this display, placebo subjects have a fewer number of administrations and shorter follow-up than subjects remaining on golimumab 50 mg or golimumab 100 mg throughout week 24. Subjects treated in early escape had the fewest number of s.c. study agent administrations and shortest follow-up.

Infections and infestations, including serious cases were the most common AE/SAE reported for golimumab across all indications. At latter time points in the studies (Week 24, or the last safety cut-off), the AE event profiles were similar to the Week 16 period. Further details for the respective indications are presented below.

Rheumatoid arthritis

Table 15 ***Number of subjects with any AEs (with frequency of ≥ 5% occurring in subjects receiving either golimumab dose) through Week 16 by MedDRA system-organ class and preferred term; treated subjects in RA Phase 3 studies.***

| | Placebo[b] | Golimumab[a] | | |
		50 mg	100 mg	Combined
Treated subjects in RA Phase 3 studies[c]	449	399	691	1089
Avg duration of follow-up (weeks)	15.6	16.0	15.9	15.9
Avg exposure (number of administrations)	3.8	3.9	3.9	3.9
Subjects with any adverse events	290 (64.6%)	270 (67.7%)	454 (65.7%)	723 (66.4%)
System-organ class/preferred term				
Infections and infestations	107 (23.8%)	108 (27.1%)	179 (25.9%)	287 (26.4%)
Upper respiratory tract infection	29 (6.5%)	25 (6.3%)	49 (7.1%)	74 (6.8%)
Gastrointestinal disorders	79 (17.6%)	80 (20.1%)	113 (16.4%)	193 (17.7%)
Nausea	19 (4.2%)	24 (6.0%)	38 (5.5%)	62 (5.7%)
General disorders and administration site conditions	52 (11.6%)	44 (11.0%)	101 (14.6%)	145 (13.3%)
Musculoskeletal and connective tissue disorders	68 (15.1%)	54 (13.5%)	82 (11.9%)	136 (12.5%)
Skin and subcutaneous tissue disorders	46 (10.2%)	41 (10.3%)	72 (10.4%)	113 (10.4%)
Nervous system disorders	36 (8.0%)	39 (9.8%)	54 (7.8%)	93 (8.5%)
Respiratory, thoracic and mediastinal disorders	47 (10.5%)	46 (11.5%)	46 (6.7%)	92 (8.4%)
Investigations	28 (6.2%)	31 (7.8%)	52 (7.5%)	83 (7.6%)
Injury, poisoning and procedural complications	21 (4.7%)	18 (4.5%)	36 (5.2%)	54 (5.0%)
Vascular disorders	6 (1.3%)	15 (3.8%)	37 (5.4%)	52 (4.8%)

a Prior to Week 16, received golimumab with or without MTX.
b Prior to Week 16, received placebo with or without MTX.
c C0524T05, C0524T06, and C0524T11.

Up to Week 16, for the SOC vascular disorders, a higher proportion of AEs were reported for golimumab (4.8%) than placebo (1.3%). This was mainly driven by hypertension, which occurred in 3.1% of subjects on golimumab and 0.7% on placebo. Hypertension is included into the SPC, and has been added to the RMP as an identified risk.

The table below shows total number of AEs, the SOC **infections and infestations** and AEs that occurred in ≥ 5% of either golimumab + MTX group in study C0524T05 through week 52.

Table 16

AE	MTX	Golimumab 100 mg	Golimumab 50 mg + MTX	Golimumab 100 mg + MTX
Total AEs reported	81%	78%	87%	87%
Infections and infestations	48%	45%	46%	48%
Upper respiratory tract infection:	13.2%	9.6%	12.7%	15%
Nasopharyngitis	4.4%	6.4%	8.2%	5.0
Influenza	6.9%	1.9%	3.2%	5.6%
Bronchitis	8.2%	5.7%	2.5%	5.6%
Nausea	16.5%	7.6%	17.7%	21.9%
Dyspepsia	7.5%	5.7%	7.6%	5.6%
Vomiting	3.8%	1.9%	5.1%	5.6%

Abdominal pain	2.5%	4.5%	6.3%	3.8%
Diarrhea	8.8%	3.2%	5.7%	3.1%
Fatigue	5.7%	6.4%	3.8%	5.6%
Injection-site erythema	0%	8.3%	6.3%	2.5%
Cough	6.3%	5.7%	3.8%	3.8%
Headache	7.5%	7.0%	3.8%	8.1%
Increase in ALT	9.4%	5.7%	17.7%	10.0%
Increase in AST	6.3%	4.5%	12.7%	6.9%
Hypertension	3.8%	3.2%	5.7%	5.6%
Rash	6.3%	4.5%	7.0%	3.8%

For e.g. nausea, vomiting, and possibly AST/ALT, there were increased incidences in groups where MTX was administered, and those are expected adverse effects of MTX.

Psoriatic arthritis

Table 17   Number of subjects with any adverse events (with frequency of ≥ 5% occurring in subjects receiving either golimumab dose) through Week 16 by MedDRA system-organ class and preferred term; treated subjects in PsA Phase 3 study

	Placebo[b]	Golimumab[a]		
		50 mg	100 mg	Combined
Treated subjects in PsA Phase 3 study[c]	113	146	146	292
Avg duration of follow-up (weeks)	15.5	15.9	16.0	16.0
Avg exposure (number of administrations)	3.7	3.9	3.9	3.9
Subjects with any adverse events	63 (55.8%)	85 (58.2%)	82 (56.2%)	167 (57.2%)
System-organ class/preferred term				
Infections and infestations	23 (20.4%)	35 (24.0%)	45 (30.8%)	80 (27.4%)
Nasopharyngitis	4 (3.5%)	6 (4.1%)	13 (8.9%)	19 (6.5%)
Upper respiratory tract infection	4 (3.5%)	11 (7.5%)	8 (5.5%)	19 (6.5%)
Gastrointestinal disorders	17 (15.0%)	18 (12.3%)	20 (13.7%)	38 (13.0%)
Musculoskeletal and connective tissue disorders	15 (13.3%)	16 (11.0%)	14 (9.6%)	30 (10.3%)
General disorders and administration site conditions	12 (10.6%)	15 (10.3%)	14 (9.6%)	29 (9.9%)
Injury, poisoning and procedural complications	7 (6.2%)	16 (11.0%)	10 (6.8%)	26 (8.9%)
Skin and subcutaneous tissue disorders	15 (13.3%)	13 (8.9%)	11 (7.5%)	24 (8.2%)
Nervous system disorders	11 (9.7%)	12 (8.2%)	11 (7.5%)	23 (7.9%)
Investigations	6 (5.3%)	8 (5.5%)	12 (8.2%)	20 (6.8%)
Respiratory, thoracic and mediastinal disorders	7 (6.2%)	12 (8.2%)	8 (5.5%)	20 (6.8%)
Vascular disorders	7 (6.2%)	9 (6.2%)	4 (2.7%)	13 (4.5%)

a Received golimumab prior to Week 16.
b Received placebo prior to Week 16.
c C0524T08.

Ankylosing spondylitis

Table 18   ***Number of subjects with any adverse events (with frequency of ≥ 5% occurring in subjects receiving either golimumab dose) through Week 16 by MedDRA system-organ class and preferred term; treated subjects in AS Phase 3 study***

| | Placebo[b] | Golimumab[a] | | |
		50 mg	100 mg	Combined
Treated subjects in AS Phase 3 study[c]	77	138	140	278
Avg duration of follow-up (weeks)	16.0	16.0	16.0	16.0
Avg exposure (number of administrations)	3.9	3.9	3.9	3.9
Subjects with any adverse events	57 (74.0%)	109 (79.0%)	106 (75.7%)	215 (77.3%)
System-organ class/preferred term				
Infections and infestations	21 (27.3%)	53 (38.4%)	51 (36.4%)	104 (37.4%)
Nasopharyngitis	9 (11.7%)	14 (10.1%)	17 (12.1%)	31 (11.2%)
Upper respiratory tract infection	4 (5.2%)	15 (10.9%)	12 (8.6%)	27 (9.7%)
Gastrointestinal disorders	15 (19.5%)	38 (27.5%)	23 (16.4%)	61 (21.9%)
Nausea	4 (5.2%)	7 (5.1%)	8 (5.7%)	15 (5.4%)
Diarrhoea	3 (3.9%)	9 (6.5%)	4 (2.9%)	13 (4.7%)
Dyspepsia	1 (1.3%)	7 (5.1%)	0 (0.0%)	7 (2.5%)
General disorders and administration site conditions	10 (13.0%)	31 (22.5%)	25 (17.9%)	56 (20.1%)
Fatigue	4 (5.2%)	11 (8.0%)	13 (9.3%)	24 (8.6%)
Musculoskeletal and connective tissue disorders	16 (20.8%)	28 (20.3%)	20 (14.3%)	48 (17.3%)
Arthralgia	7 (9.1%)	10 (7.2%)	5 (3.6%)	15 (5.4%)
Back pain	2 (2.6%)	8 (5.8%)	2 (1.4%)	10 (3.6%)
Nervous system disorders	7 (9.1%)	23 (16.7%)	19 (13.6%)	42 (15.1%)
Headache	2 (2.6%)	11 (8.0%)	8 (5.7%)	19 (6.8%)
Dizziness	3 (3.9%)	9 (6.5%)	4 (2.9%)	13 (4.7%)
Respiratory, thoracic and mediastinal disorders	9 (11.7%)	24 (17.4%)	15 (10.7%)	39 (14.0%)
Cough	4 (5.2%)	8 (5.8%)	4 (2.9%)	12 (4.3%)
Pharyngolaryngeal pain	3 (3.9%)	8 (5.8%)	4 (2.9%)	12 (4.3%)
Skin and subcutaneous tissue disorders	9 (11.7%)	21 (15.2%)	17 (12.1%)	38 (13.7%)
Investigations	5 (6.5%)	13 (9.4%)	21 (15.0%)	34 (12.2%)
Alanine aminotransferase increased	2 (2.6%)	6 (4.3%)	12 (8.6%)	18 (6.5%)
Aspartate aminotransferase increased	1 (1.3%)	4 (2.9%)	11 (7.9%)	15 (5.4%)
Eye disorders	3 (3.9%)	10 (7.2%)	7 (5.0%)	17 (6.1%)
Psychiatric disorders	4 (5.2%)	7 (5.1%)	8 (5.7%)	15 (5.4%)
Injury, poisoning and procedural complications	5 (6.5%)	6 (4.3%)	8 (5.7%)	14 (5.0%)

a Received golimumab prior to Week 16.
b Received placebo prior to Week 16.
c C0524T09.

- Serious adverse event/deaths/other significant events

Deaths
A total of 13 subjects died during the golimumab studies through the latest safety data cut-off (June 2008); 12 of which with golimumab. In the original application, 9 deaths were reported, and 8 of those were in subjects treated with golimumab (3 related to infection, one malignancy, one cerebral hemorrhage, one suicidal event, one tramadol overdose, one climbing accident). There were also four cases on golimumab reported after the last safety cut-off (two from C0524T06, and two from C0524T05. Among these deaths, there were infections, malignancy, cardiac and hepatic events which were possibly related to golimumab treatment. In 3 cases accidents/suicide, were non-related.

Serious adverse events
At latter time points in the studies (last safety cut-off of the initial application, September 2007), the SAE event profiles were similar to the Week 16 and Week 24 period, although some, e.g. infections like TB or malignancies, were only observed after longer duration than 16 Weeks (see below). Some SAEs are presented in more detail below, for the respective group of events.

Rheumatoid arthritis
Through Week 16 in the Phase 3 RA studies, the proportions of subjects who had at least 1 SAE was 4.7%, 5.5%, and 3.8% in the placebo, golimumab 50 mg, and golimumab 100 mg groups, respectively. Sepsis (sepsis and urosepsis) and pneumonia occurred more frequently in golimumab-treated subjects (1 (0.3%) and 1 (0.3%) on golimumab 50 mg and 4 (0.6%) and 2 (0.3%) on golimumab 100 mg, respectively) compared with none on placebo. Through Week 24, despite shorter placebo follow-up, SAEs and pneumonia frequencies were similar for placebo and both golimumab doses, while sepsis occurred more frequently with golimumab (1 (0.3%) on golimumab 50 mg, 5 (0.7%) on golimumab 100 mg) compared with none on placebo.

In the C0524T05 study through Week 52, the MTX group (13.2%) had a higher proportion of SAEs compared with golimumab 100 mg (5.1%) or golimumab + MTX (9.5% golimumab 50 mg + MTX and 8.8% golimumab 100 mg + MTX). The most frequently occurring SAE was pneumonia (2 (1.3%) subjects on MTX, 1 (0.6%) on golimumab 100 mg and 2 (1.3%) on golimumab 100 mg + MTX).

Psoriatic arthritis
Both through Week 16 and 24, SAEs were reported less frequently in the combined golimumab group (1.7% and 2.0%) than for the placebo group (5.3% and 6.2%). The proportions of subjects with SAEs in the combined golimumab group were generally similar regardless of MTX use at baseline.

Ankylosing spondylitis
Through Week 16, the proportion of subjects reported with SAE was 4.3% in the combined golimumab group and 5.2% on placebo. Through Week 24, it was 5.4% in the combined golimumab group and 6.5% on placebo, and generally similar regardless of DMARDs use at baseline.

Infections
Across the indications, the pattern and types of infections through Week 24 were similar as through Week 16. The proportion of subjects who had an infection requiring antimicrobial treatment was increased in golimumab treated subjects in all studies. Generally, the most frequently occurring infection was upper respiratory tract infection.

Serious, including opportunistic infections
The incidences per 100 subject-years of follow-up across all Phase 2b and 3 studies for the 3 most common serious infections, sepsis, pneumonia, and cellulitis are shown in the Table below.

Table 19 Frequency of infections in rheumatologic indications through the last safety cut off in the initial application (September 2007)

Event	All three rheumatologic indications (Phase 2b, 3 studies)		
event rate (CI)	Placebo	Golimumab 50 mg	Golimumab 100 mg
Sepsis *	0.32 (0.01, 1.77)	0.36 (0.07, 1.05)	0.99 (0.47, 1.82)
Pneumonina*	2.86 (1.31, 5.43)	2.16 (1.28, 3.41)	1.48 (0.83, 2.45)
Cellulitis *	1.59 (0.52, 3.71)	2.16 (1.28, 3.41)	1.98 (1.21, 3.05)

* The following MedDRA terms were used for **sepsis:** *sepsis, urosepsis, and septic shock;* **pneumonia**: *pneumonia, bronchopneumonia, lobar pneumonia, Legionella pneumonia, streptococcal pneumonia, bacterial pneumonitis, and viral pneumonitis*; **cellulitis**: *cellulitis.*

Through the safety cut-off of the Phase 3 studies, the most common serious infection in golimumab-treated subjects was sepsis. Other types of serious infections observed included hepatomegaly and toxic hepatitis classified by the investigator as infections, abscess, acute cholecystitis, infectious mononucleosis, and otitis media chronic. Across all studies, one opportunistic infection was observed; a Legionella pneumonia in the Phase 2b RA study with golimumab 100 mg q4w. In the updated safety data base, one case of liver histoplasmosis was reported after Week 52 in study C0524T08.

In the five Phase 3 studies through Week16, subjects on corticosteroids at baseline were more likely to have a serious infection (1.4% placebo, 2.1% golimumab 50 mg, 2.5% golimumab 100 mg) compared with subjects who did not receive corticosteroids at baseline (1.1% placebo, 0.3% golimumab 50 mg, 1.1% golimumab 100 mg).

Through the latest safety cut off (June 2008) in the five Phase 3 studies, there were seven cases of tuberculosis (TB) reported. Among the five cases in the original application, four occurred in RA studies and one in the Asthma study. Among RA patients there were 2 subjects with pulmonary TB (1 on 50 mg, 1 on 100 mg), 1 subject had bone TB (50 mg), and 1 tuberculous pleurisy (50 mg) and 1 had lung/pleural and questionable ileal tuberculosis (100 mg). One TB case in the severe asthma study was a case with pleural involvement (100 mg). According to the inclusion criteria in the Phase 3 studies, appropriate treatment of latent TB should have been initiated before or simultaneously with golimumab treatment in patients where such treatment was considered warranted. The Applicant has discussed effects on liver function tests, and in this discussion it is stated that 319 (13.9%) subjects required treatment for latent TB across the five Phase 3 studies, and that the vast majority of these subjects received isoniazid (INH) therapy. Further detail on anti-TB treatment undertaken in the clinical studies were provided. In about two thirds of subjects who got anti-TB treatment, it was started prior to golimumab administration, while nearly 30% started treatment simultaneously with and 6% started treatment after golimumab treatment. So far, there has been no report of development of active TB during golimumab treatment in subjects given anti-TB treatment. Although these data are limited, they provide some reassurance regarding use of golimumab in subjects who are treated for suspected latent TB, and support the recommendations in the SPC that golimumab treatment may be considered if latent TB is treated.

Close monitoring, and adequate information are of great importance to minimise the risk for development of TB in association with use of an anti-TNF agent. Adequate measures have been addressed in the RMP, including an education programme.

Possible Anaphylactic or Serum Sickness-like Reactions
There were no anaphylactic or serum sickness-like reactions in golimumab-treated subjects across the Phase 3 studies, while one case of serum sickness was reported in the severe asthma study. Small proportions of subjects had nonspecific AEs of rash, urticaria, and hypersensitivity, with slightly higher incidences for golimumab. Thus, the occurrence of less serious allergic reactions cannot be excluded, although the data do not indicate a clear increase of allergic reactions.

Neoplasms/Malignancies
The following Table shows the incidence of malignancies per 100 subject-years during the placebo-controlled portions of all Phase 2b and 3 studies.

Table 20   Incidence of malignancies per 100 subject-years during placebo-controlled portions of all Phase 2b and Phase 3 studies

Event rate (CI)	All three rheumatologic indications (phase 2b, 3 studies)		Phase 2b severe asthma	
	Placebo	**Combined golimumab**	**Placebo**	**Combined golimumab**
Lymphoma	0.0 (0.0, 0.96)	0.21 (0.03, 0.77)	0.0 (0.0, 2.94)	0.40 (0.01, 2.20)
Nonmelanoma skin cancers	1.29 (0.35, 3.30)	0.75 (0.30, 1.54)	0.0 (0.0 2.94)	0.79 (0.10, 2.86)
Other malignancies	0.64 (0.08, 2.32)	0.43 (0.12, 1.09)	0.0 (0.0, 2.94)	1.99 (0.64, 4.63)
All malignancies	1.93 (0.71, 4.21)	1.39 (0.74, 2.37)	0.0 (0.0, 2.94)	3.19 (1.38, 6.28

The uncertainties related to long-term use of TNF-alpha inhibitors and the potential risk for malignancy are well known concerns associated with use of these products. In the placebo controlled phases of the studies in rheumatologic indications, there was an increased incidence of lymphoma in golimumab treated patients, while the incidence of non-melanoma skin cancers and other malignancies was increased in the placebo groups. The observational time period (24 -52 weeks) is too short to draw definite conclusions.

The findings in the 52 weeks study in severe, persistent asthma, with no malignancy among placebo subjects (n=78, 0%), and 8 cases among golimumab treated subjects (n= 231, 3.5%) raise serious concern, although the different patient population and the use of higher doses than applied for in this application are acknowledged. Following analyses of these findings in more depth, no obvious explanation has been established. These results thus remain a concern. In this context, the findings with infliximab in an exploratory clinical study involving patients with moderate to severe COPD who all had a history of heavy smoking should be noted. In this study, 157 patients were treated with infliximab at doses similar to those used in RA and Crohn's disease. Nine of these patients developed malignancies. The median duration of follow-up was 0.8 years (incidence 5.7% [95% CI 2.65% - 10.6%]. There was one reported malignancy amongst 77 control patients (median duration of follow-up 0.8 years; incidence 1.3% [95% CI 0.03% - 7.0%]). The majority of the malignancies developed in the lung or head and neck. It is therefore of importance that 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. This information is provided in the SPC also for golimumab. It is currently unknown whether there is any association between these lung diseases and risk for malignancy with use of an anti-TNF agent. With respect to the rheumatologic populations, there is no such clear signal within the considerably more extensive database. As for all anti-TNF agents, the potential risk for malignancy has to be weighed against the potential benefit of golimumab therapy in the indications applied for. The risk of malignancies has been addressed in the SPC and relevant risk minimisation and pharmacovigilance activities are part of the RMP.

Autoimmune Disorders, Antinuclear Antibodies/Double-stranded DNA Antibodies
For golimumab, and across the five Phase 3 studies through the last safety cut-off in the initial application (September 2007) there was one case of systemic lupus erythematosus, and one lupus-like syndrome. There were 5 cases of pustular psoriasis, and 2 reports of vasculitis. Overall, these types of AEs have been observed with other anti-TNF agents. The SPC contains relevant information. Psoriasis (new onset and pustular) has been included in the Table in section 4.8.

The proportion of subjects who were negative for antinuclear antibodies (ANA) at baseline, but who had a newly positive ANA test result during the Phase 3 studies, was increased in the majority of golimumab groups in RA studies, compared with placebo, but not in the PsA or AS studies. There were few cases (3) that newly tested positive for anti-dsDNA antibodies. Relevant information has been added to the SPC.

Hepatobiliary Adverse Events
As of the last safety cut-off (September 2007) in the initial application for the combined RA, PsA, and AS studies, there were 6 (0.9%) subjects in the placebo group, 10 (0.8%) subjects on golimumab 50 mg, and 26 (2.4%) subjects on golimumab 100 mg with a hepatobiliary AE. The type of hepatobiliary events remained similar to what was observed through Week 16 and 24.

Laboratory test results have shown some cases of patients experiencing >8xULN ALT increase. Most of them were transitory and asymptomatic, and there is no need for liver function test (LFT) monitoring. Information on liver enzyme elevations has been added in the SPC, and hepatic events is addressed in the RMP.

A panel of 4 external hepatologists reviewed and adjudicated twelve cases (9 golimumab and 3 placebo) of hepatobiliary AEs in 11 subjects that were considered as clinically important. Out of these reports, 2 were considered probably related and 6 possibly related judged by the expert panel. The numbers of significant events were low, where 3 patients discontinued golimumab permanently. Two patients made a temporary interruption indicating less severe symptoms. One fatal case of fulminant hepatitis has been reported with golimumab 100 mg in a 24 year old female patient with history of LFT abnormalities and Hashimoto's disease (C0524T06-5805-60659). Although the involvement of golimumab is uncertain, this case is reflected in the SPC.

Pulmonary Adverse Events of Interest
Through the safety cut-off, for the five Phase 3 studies, there was one SAE of interstitial lung disease (golimumab + MTX), four subjects reporting pneumonitis (2 MTX, 2 golimumab + MTX), and one SAE of fibrosing alveolitis (golimumab + MTX). All these events occurred in RA trials. Associations to MTX cannot be excluded, given its known relation to pulmonary AEs.

Cardiovascular safety
In the AS study, there was a higher number of 'cardiac disorders' in the golimumab groups vs. placebo (0 placebo vs. 6 (2.2%) combined golimumab group; 2 angina pectoris/unstable, 1 cardiac flutter, 1 myocardial infarction, 2 palpitations, 1 tachycardia). In contrast, there was no increase in the RA or PsA studies. Further analyses of these data suggested that most of these subjects had pre-existing cardiac disease, and a role of golimumab is not clearly evident. However, arrhythmia and ischemic coronary artery disorders have been added to the SPC, section 4.8.

In all Phase 3 studies, except study CO524T08, more patients had vascular disorders when treated with golimumab than placebo. This difference was mostly due to the adverse event hypertension. Following further review of all hypertension cases reported in golimumab treated patients, it is agreed that there is no need to add specific recommendations for patients with known hypertension, or regarding blood pressure monitoring in the SPC. Still, hypertension should be further monitored as outlined in RMP, and is mentioned in the SPC, section 4.8.

Through the safety cut-off for the five Phase 3 studies, 2 subjects had events of congestive heart failure (CHF) with golimumab. In the golimumab Phase 3 trials, subjects with a history of or concurrent CHF including medically controlled, asymptomatic CHF were excluded. Given the exclusion criteria there is a lack of data in a population with CHF. This aspect together with the findings in the Phase 2 study with another anti-TNF agent, where treatment lead to worsening of CHF and a number of fatalities, clearly justify a contraindication of patients with moderate to severe heart failure (NYHA class III/IV) and a special warning for use of golimumab in CHF. Congestive heart failure should be further monitored as outlined in the RMP, and is mentioned in the SPC.

Psychiatric disorders
Through the latest safety cut-off (June 2008), there have been six cases of suicide attempt/ideation; one of those committed suicide. Through Week 24, psychiatric AE occurred in 4.2% of placebo subjects and 5.3% of all golimumab-treated (most commonly insomnia, depression, and anxiety). Although there is no strong signal for an increased incidence of psychiatric AEs with golimumab, information related to depression and insomnia has been added to the SPC and addressed in the RMP.

Demyelinating Disorders
In the Phase 3 studies, there was one SAE of demyelination, which is a known class effect for anti-TNF agents. Relevant warnings have been added to the SPC.

Injection-site reactions
During the placebo controlled phases in the Phase 3 studies there was a higher incidence of injection

site reactions associated with golimumab (3.4 - 6.7% across studies) than with placebo (2-2.7% across studies). In the majority of cases, reactions were mild or moderate. Up to Week 24, there was only one event of severe injection-site erythema. Across the Phase 3 studies, a higher proportion of injection-site reactions were observed in subjects who were positive for antibodies to golimumab (7 subjects, 12.3%) compared with subjects who had negative (14 subjects, 7.1%) or 'undetectable' results (88 subjects, 8.2%). Since the amount of data is rather small, only limited conclusions can be drawn. There is no indication of severe/serious reactions linked to the development of antibodies. Relevant information has been included in the SPC, including information from 52 weeks of treatment.

Immunological events
The overall incidence of antibodies was 4.3% across all subjects treated in Phase 3 studies with similar rates in each rheumatologic indication. The antibody incidence was similar for subjects receiving 50 mg + MTX (1.7%) compared with subjects receiving 100 mg + MTX (1.9%). Treatment with concomitant MTX resulted in a lower proportion of subjects with antibodies to golimumab than subjects receiving golimumab without MTX (approximately 2% versus 7%, respectively), although this was only evaluated in a randomized manner for subjects receiving golimumab 100 mg in C0524T05 and C0524T06. Approximately half of the antibody responses observed in the Phase 2 RA study were neutralizing as measured by a cell-based functional assay. A summary of antibody data at Week 52 from C0524T05, C0524T06 and C0524T08 show a similar pattern as seen at Week 24, although the overall incidence was higher (5.2%). When looking at potential impact of antibodies on efficacy, Week 52 data from C0524T05 indicated that efficacy appeared to be reduced in subjects positive for antibodies. However, a summary of data from C0524T05, C0524T06 and C0524T08, does not show a clear-cut relationship between presence of antibodies and reduced efficacy. With respect to safety, there was a slightly higher incidence of injection reactions in subjects positive for antibodies compared with those being negative or inconclusive. These findings are reflected in the SPC.

- Laboratory findings

Across the three indications, there were no unexpected findings in haematology or chemistry evaluations, with the exception of some elevations in hepatic function parameters and some cases of significant decreases of neutrophils reported one or more times in patients while treated with golimumab. Decreased neutrophiles has been added to the SPC, section 4.8.

- Safety in special populations

The experience in pregnancy (9 pregnancies and 9 pregnancies in partners) is far too limited to draw any conclusions. The product information has been worded in line with other anti-TNF agents.

- Safety related to drug-drug interactions and other interactions

In the Psoriatic arthritis study, effects on pneumococcal vaccination were monitored. There was no difference in the vaccine response between subjects treated with placebo or golimumab, while concomitant use of MTX was associated with reduced vaccine response. Relevant information has been included in the SPC, section 4.4.

- Discontinuation due to adverse events

The discontinuation pattern does not raise concerns related to either efficacy or safety, and is not considered to have had a negative impact on the interpretation of the studies' results. The total number of subjects who discontinued is overall relatively low.

- Post marketing experience

At the time of Marketing Authorization, no postmarketing experience was available for golimumab.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 21: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Identified risk		
Serious infections including opportunistic infections and TB (class effect)	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional PV activities** • TB follow-up questionnaire **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** Guidance is provided in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SPC. **Additional activities** • Patient Alert Card • Golimumab Educational Program
Demyelinating disorders (class effect)	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** Demyelinating disorders are included in the Special Warnings and Precautions for Use and Undesirable Effects sections of the SPC. **Additional activities** None
Hypertension	**Routine PV activities** • AE collection and single case	**Routine Activities** Hypertension is included in the

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
	processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	Undesirable Effects section of the SPC **Additional Activities** none
Potential risks		
Malignancy	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional PV activities** • Lymphoma follow-up questionnaire **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** Guidance is provided in the Special Warnings and Precautions for Use and Undesirable Effects sections of the SPC. **Additional activities** None
Serious hepatotoxicity	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** Elevations in transaminases are described in the Undesirable Effects section of the SPC. Guidance is also provided in the Posology and method of administration and the Special Warnings and Precautions for Use sections of the SPC. **Additional activities** None

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Exposure during pregnancy	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • Pregnancy Research Initiative • RABBIT • i3 Drug Safety Epidemiology Study	**Routine activities** Guidance is provided in Section 4.6, Pregnancy and Lactation, of the SPC. **Additional activities** None
HBV reactivation (class effect)	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** A statement regarding severe infections is included in the Contraindications section of the SPC; HBV reactivation is included in the Special Warnings and Precautions for Use and Undesirable Effects sections of the SPC. **Additional activities** • Patient Alert Card • Golimumab Educational Program
CHF (class effect)	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** CHF is described in the Contraindications, Special Warnings and Precautions for Use and Undesirable Effects sections of the SPC. **Additional activities** • Patient Alert Card • Golimumab Educational Program
Serious systemic hypersensitivity	**Routine PV activities**	**Routine activities**

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
(anaphylaxis and serum sickness; class effect)	• AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	None **Additional activities** • Golimumab Educational Program
Autoimmune processes (class effect)	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • RABBIT • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	**Routine activities** Autoimmune processes are described in the Special Warnings and Precautions for Use and Undesirable effects sections of the SPC. **Additional activities** None
Maladministration/administration error	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection • Product information	**Routine activities** Instructions for administration are provided in the Posology and method of administration section of the SPC and detailed instructions for patients on administration techniques are provided in the Package Leaflet of the SPC. **Additional activities** • Golimumab Educational Program
Serious depression including suicidality	**Routine PV activities** • AE collection and single case processing • Aggregate reports: Periodic Safety reporting • Surveillance and signal detection	**Routine Activities** Depression is included in the Undesirable Effects section of the SPC **Additional Activities** none

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
	• Product information **Additional clinical trial data** • Long-term extensions of Phase 3 RA, PsA, and AS studies • Other Phase 2/3 studies **Registry and Epidemiology studies** • Swedish Database Initiative • i3 Drug Safety Epidemiology Study	

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in the Annex "Conditions or Restrictions with regard to the Safe and Effective Use of the Medicinal Product to be implemented by the Member States".

2.6   Overall conclusions, risk/benefit assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance are adequately described, controlled and validated. The drug substance is well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications are set. The manufacturing process of the drug product has been satisfactorily described and validated. The quality of the drug product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of points, which will be addressed as part of post-approval follow-up measures, the overall Quality of Simponi is considered acceptable.

Non-clinical pharmacology and toxicology

The non-clinical testing strategy to support development of golimumab was designed and conducted in accordance with the ICH S6. Due to species specificity of golimumab, the cynomolgus monkey was chosen as the most relevant non-clinical species for pharmacology and toxicology studies. In addition, studies in mice using an analogous anti-mouse TNFα monoclonal antibody, cV1q, were provided as supporting data.

Being a monoclonal antibody, no genotoxicity or carcinogenicity studies or environmental risk assessment have been performed with golimumab. This is according to current guidelines for biotechnology-derived pharmaceuticals (ICH S6) and was considered acceptable.

The non-clinical data presented reveal no special hazard for humans. In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. This information is reflected in the SPC.

Efficacy

Rheumatoid Arthritis (RA)
In RA a dose-finding study and three Phase 3 studies were performed. The dose-finding study concluded that two doses were appropriate to include in the following development program in RA. The chosen doses were 50 mg and 100 mg every fourth week (q4w). The rationale for this choice is not fully obvious, and a lowest effective dose has not been defined. A lower dose than what was included in the dose-finding study might have been considered. Although a consistently lower efficacy with monotherapy was found in the three pivotal RA studies, there is insufficient evidence for the lowest effective dose. Still, it is considered that there is sufficient support for the proposed posology

Among the three RA studies, there was one study in active RA despite methotrexate (MTX) (C0524T06) with a similar population as in the pivotal trials for all previously approved anti-TNFs agents. The second study (C0524T05) included patients with active RA but naïve to MTX; MTX was introduced at baseline. The third study (C0524T11) included patients who had been treated with at least one dose of anti-TNF before inclusion. The submitted documentation presented study data up to 24 weeks duration of the studies. Fifty-two weeks x-ray data from Study T06 were not presented in this application.

In study C0524T06 444 RA patients with active disease despite MTX were randomised to four treatment groups. MTX was combined with 50 mg or 100 mg golimumab or with placebo and in one group MTX was discontinued. The study population was similar to previous approvals, with respect to baseline disease activity and characteristics. The primary efficacy endpoint ACR20 (20% decrease in activity) showed significant results in the two groups of golimumab 50 mg and 100mg in combination with MTX. However, monotherapy with golimumab 100 mg was not significantly different from placebo+MTX.

In study T05, 637 MTX-naïve patients were randomised to four treatment groups. MTX was introduced at baseline in three of the groups together with golimumab 50mg and 100 mg and placebo. In the fourth group monotherapy with golimumab + placebo was introduced. ACR50 (50% decrease in activity) was chosen as the primary endpoint, which is a more strict criterion than in previous anti-TNF approvals. ACR50 did not reach statistical significant difference towards placebo. However, ACR20 reached significantly different effect versus placebo.
Study C0524T11 included patients who had been treated with at least one dose of an anti-TNF prior to study participation. The study design did not define a treatment refractory population, as reasons for discontinuing the anti-TNF agent were not defined strictly. This three-arm study, where MTX or sulphasalazine or hydroxychloroquine were accepted as concomitant medications, showed significant results for the primary endpoint, ACR20 at Week 14 for golimumab 50 and 100 mg.

In all three studies, there was no improved efficacy with 100 mg compared with 50 mg. Efficacy with combination therapy with MTX was consistently better than monotherapy.

Psoriatic Arthritis (PsA)
One Phase 3 study in subjects with PsA has been submitted, where 50 and 100 mg golimumab given every 4 weeks was compared to placebo. The primary efficacy analyses were undertaken after 16 weeks. Thereafter, subjects who did not meet defined response were eligible to early escape.

The population included had moderate to severe PsA activity. The majority of subjects had taken one or more DMARDS for PsA (75-80% in all groups), had prior exposure to topical treatments for psoriasis, but not to systemic psoriasis medications. About half of the subjects were taking MTX at baseline at a median dose of 15 mg/week. Overall, this population is considered relevant for studying effects on PsA of an anti-TNF agent. The majority of subjects had $\geq$ 3% BSA involvement with psoriasis; the median BSA in these subjects was 8-10% (range 3-99). This corresponds to mild psoriasis, which is reflected in the SPC.

The study design, selected endpoints and analyses undertaken are considered relevant for the intended aim of the study. Overall, the discontinuation pattern does not raise concern, and is not considered to

have a negative impact on the study interpretation. It was shown that both dose levels of golimumab statistically significantly improved signs and symptoms after 16 weeks, based on number of ACR20 responders. Several sensitivity analyses showed that the results were robust, and secondary endpoints supported this finding. Overall, there is convincing evidence of efficacy in the short term.

Subgroup analyses were possible to undertake for two subtypes of PsA, asymmetrical and polyarticular disease. Statistically significant efficacy (ACR20) was shown in both of these subgroups. Information on subgroups in the study is described in the SPC.

Ankylosing spondylitis (AS)
One Phase 3 study in subjects with AS has been submitted, where 50 and 100 mg golimumab q4w was compared to placebo. The primary efficacy analyses were undertaken after 16 weeks. Thereafter, subjects who did not meet defined response criteria were eligible to early escape.

Based on various parameters addressing disease activity, it can be concluded that subjects in all groups had a moderately high level of pain and inflammation. At baseline, more than 99% of the subjects were receiving NSAIDs, and the proportions of subjects using other medications for AS were generally similar across all groups. Approximately two thirds of subjects had a screening CRP level of ≤ 1.5 mg/dl, and the median CRP level at baseline for the combined golimumab group was 1.0 mg/dl. Overall, this population is considered relevant for studying effects on AS of an anti-TNF agent.

Overall, the discontinuation pattern does not raise concern, and is not considered to have a negative impact on the study interpretation. Golimumab, combined groups, resulted in significantly greater number of subjects achieving an ASAS 20 response Week 14. The response was numerically greater for each golimumab dose group in the higher CRP stratum compared with the lower. All sensitivity analyses supported the results of the primary endpoint analysis. Further support of efficacy was obtained by a number of secondary endpoint analyses. However, there was no significant effect on the BASMI score, addressing mobility, even if some subscores as well as chest expansion were statistically significantly improved. Although one expectation with successful treatment is improvement in spinal mobility, the treatment period may be too short to results in significant improvement of these parameters. Overall, efficacy in the short term has been demonstrated.

However, long-term data are lacking, which is a major shortcoming. As outlined in the draft guideline (CHMP/EWP/4891/03), although efficacy may be demonstrated in a 12-24 weeks trial, maintenance of the effect in longer trials (e.g. 1 year) should be demonstrated.

The majority of subjects tested positive for the HLA-B27 antigen. Thus, although subgroup analyses suggested efficacy also in subjects negative for HLA-B27 antigen, experience in this subgroup is limited.

Safety

In total 2154 subjects have been exposed to golimumab, approximately half at each dose level of 50 and 100 mg, across the three indications. The numbers of subjects exposed for at least 6 months in the different indications are 1180 (RA), 472 (PsA), 325 (AS), and for at least 12 months were 512 (RA); 254 (PsA) and 160 (AS). These numbers are sufficient to meet ICH recommendations, for all indications. During the review process, additional safety data were submitted, with a data cut-off of June 2008.

As expected, the adverse event profile, across the three populations, is similar to that for other anti-TNF agents. Infections and infestations, including serious cases were the most common AE/SAE reported for golimumab across all indications. At latter time points in the studies (week 24, or the last safety cut-off), the AE event profiles were generally similar to the week 16 period, although some e.g. infections like TB, or malignancies were only observed after longer duration than 16 weeks.

A total of 13 subjects died during the golimumab studies through the latest safety data cut-off; of which 12 with golimumab. Among those, 9 were judged as possibly related, and due to infection, cardiac or hepatic events.

Through the safety cut-off of the phase 3 studies, the most common serious infection in golimumab-treated subjects was sepsis. Other types of serious infections observed included hepatomegaly and toxic hepatitis classified by the investigator as infections, abscess, acute cholecystitis, infectious mononucleosis, and otitis media chronic. Across all studies, one opportunistic infection was observed. In the updated safety data base, one case of liver histoplasmosis was reported after W52 in study C0524T08. Through the latest safety cut off (June 2008) in the five phase 3 studies, there were seven cases of TB reported. The SPC contains relevant warnings and precautions related to infections.

The uncertainties related to long-term use of TNF-alpha inhibitors and the potential risk for malignancy are well known concerns associated with use of anti-TNF agents. In the placebo controlled phases of the studies in rheumatologic indications, there was an increased incidence of lymphoma in golimumab treated patients. Through the latest cut-off, there was increased numbers of neoplasms such as skin cancer, squamous cell carcinoma and melanocytic naevus, which is included as an uncommon adverse reaction in the PI. Relevant risk minimisation and pharmacovigilance activates are also to be undertaken post marketing.

In the AS study only, there was a higher number of *'cardiac disorders'* in the golimumab groups vs. placebo (0 placebo vs. 6 (2.2%) combined golimumab group. Although most of these subjects had pre-existing cardiac disease, the role of golimumab is not clearly evident. Still, cardiac disorders should be further monitored. In all phase III studies, except C0524T08, more patients had vascular disorders when treated with golimumab than placebo. This difference was mostly due to the hypertension. Two subjects had congestive heart failure (CHF) with golimumab. Cardiovascular safety is addressed in the SPC.

In the RA and AS studies through Week 16, ALT elevations ≥ 5 x ULN were seen in more golimumab-treated patients (0.4% to 0.9%) than controls (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 golimumab-treated and control patients in all Phase III studies. One patient with pre-existing liver abnormalities and confounding medication treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded. Relevant wording regarding liver safety has been included in the SPC.

There were no anaphylactic or serum sickness-like reactions in golimumab-treated subjects across the phase 3 studies, while one case of serum sickness was reported in the severe asthma study. Small proportions of subjects had nonspecific AEs of rash, urticaria, and hypersensitivity, with slightly higher incidences for golimumab. Thus, the occurrence of less serious allergic reactions cannot be excluded, although the data do not indicate a clear increase of allergic reactions.

During the placebo-controlled phases, psychiatric AE occurred in 3.6% patients on placebo, and in 3.4% for all golimumab treated. Through Week 24, psychiatric AE occurred in 4.2% of placebo subjects and 5.3% of all golimumab-treated (most commonly insomnia, depression, and anxiety). Although there is no strong signal for an increased incidence of psychiatric AEs with golimumab, information is added to the PI, and addressed in the RMP.

In the phase 3 studies, there was one SAE of demyelination, which is a known class effect for anti-TNF agents. The SPC contains relevant information.

Through 1 year of follow up, 4.0% of golimumab-treated patients and 2.6% of control patients were newly ANA-positive (at titers of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow up in patients anti-dsDNA negative at baseline was uncommon. There was one case of systemic lupus erythematosus, and one lupus-like syndrome. There were 5 cases of pustular psoriasis, and 2 reports of vasculitis.

Overall, the profile of golimumab is similar to that of other TNF-alpha blockers and the SPC is in line with those of other anti-TNF agents with respect to sections 4.4 and 4.8. Furthermore, the RMP addresses the safety concerns noted above.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A user consultation was conducted and judged acceptable.

Risk-benefit assessment

Benefits:

Rheumatoid Arthritis
Studies C0524T06 and C0524T11, where golimumab was given as add-on to MTX, had the same study design (early escape at Week 16) and the same primary endpoint (ACR 20 response at Week 14). Study populations were also similar, although in C0524T11, subjects should have been exposed to at least one dose of an anti-TNF agent. Controlled data of up to 24 weeks duration were submitted originally, and based on those data, it can be concluded that statistically significant and clinically relevant efficacy has been shown. Although only uncontrolled data from week 24 to 52 were submitted from C0524T06 which are difficult to interpret due to a number of treatment changes in all groups, and no new data was available from C0524T11, it can be concluded that the Week 24 data are sufficiently convincing to support approval, and there is no indication of unexpected effects through Week 52. The lack of x-ray data are considered acceptable for a second line indication, since there is sufficient indirect evidence for no deleterious effects on the joints (e.g. data from other anti-TNFα agents, support for a relationship between CRP, tender and swollen joints and radiologic progression). Thus, it can be concluded that efficacy has been demonstrated to support indications in RA subjects with inadequate response to previous DMARDs. However, it is not accepted to mention in the indication that golimumab can be used in subjects previously treated with one or more TNF inhibitor(s).

In study C0524T05, golimumab, as monotherapy or combination with MTX, was tested against MTX in treatment naïve RA patients. The original application contained 24 weeks data, and subsequently, controlled data on signs and symptoms up to Week 52 were submitted. InC0524T05, statistical significance was not met for the primary endpoint, ACR50 at Week 24. However, the ACR20 results were statistically significant and the p-value for ACR50 response was at borderline significance. Other secondary measures were in favour of combination therapy with golimumab 50 mg + MTX once a month. Controlled data through Week 52 from study C0524T05 on signs and symptoms have also been submitted. Analyses for ACR50 and ACR20 resulted in statistically significantly differences between golimumab combined and MTX. However, the 50 mg+ MTX dose was not statistically different from MTX, and the observed differences were small (ACR50 6.5%; p=0.235; ACR20 7.8%, p=0.157). It is acknowledged that the observed differences appear to be almost of the same magnitude as seen for the other anti-TNF agents in this population, which have an indication in severe, active and progressive RA for subjects treatment naïve to MTX. However, in contrast to these products for which 52 and/or 104 weeks x-ray data were available that showed a beneficial effect on joint damage in support of such indication, no data on structural damage is available for golimumab. Furthermore, these products also had 2 years x-ray data in the second line population showing a similar pattern. Thus, approval of treatment naïve RA is not accepted based on available data.

Taken together, golimumab in combination with MTX, showed clinically relevant efficacy on signs and symptoms in relevant patient populations. Efficacy with golimumab 100 mg monotherapy is surprisingly low and only combination therapy is reflected in the indication. X-ray data are still

lacking, which precludes approval for use in treatment naïve patients. Overall, the effect size appears comparable to that of other anti-TNF agents, although head-to head comparisons are lacking which is a shortcoming.

Psoriatic arthritis
In the PsA study, it was shown that both dose levels of golimumab statistically significantly improved signs and symptoms after 16 weeks, based on number of ACR20 responders (9%, 51% and 45% in the placebo, 50 and 100 mg groups, respectively). Several sensitivity analyses showed that the results were robust, and secondary endpoints supported this finding. The effect size appears comparable to that of other anti-TNF agents. Overall, there is convincing evidence of efficacy in the short term. During the review process, the applicant has submitted uncontrolled data up to Week 52. Due to the different changes of treatments for a number of patients in all groups (early escape or cross over), these are difficult to interpret. However, it is considered that the Week 24 data are sufficiently convincing, and there is no indication of unexpected effects by Week 52. The lack of x-ray data are considered acceptable for this indication since there is sufficient indirect evidence for no deleterious effects on the joints. Thus, efficacy has been demonstrated to support indications in PsA subjects with inadequate response to previous DMARDs.

Subgroup analyses were possible to undertake for two subtypes of PsA, asymmetrical and polyarticular disease. Statistically significant efficacy (ACR20) was shown in both of these subgroups. Information on subgroups in the study is described in the SPC.

The results point to a slightly better effect with the combination golimumab + MTX compared with monotherapy, and antibodies were only identified in subjects in the non-MTX stratum during the 24 weeks period of the study. However, differences are not considered of significant clinical relevance, and comparable with results seen for other anti-TNFs. Thus, a monotherapy option is accepted.

Ankylosing spondylitis
Golimumab, combined groups, resulted in significantly greater number of subjects achieving an ASAS 20 response at Week 14. The response was numerically greater for each golimumab dose group in the higher CRP stratum compared with the lower. All sensitivity analyses supported the results of the primary endpoint analysis. Further support of efficacy was obtained by a number of secondary endpoint analyses. Overall, efficacy in the short term has been demonstrated for this indication. Long-term data from the other indications are sufficiently supportive to recommend approval of this indication.

Other DMARDs were allowed as concomitant therapy in the AS study, although 68% of subjects did not have such treatment. An analysis submitted by the applicant did not show any difference in response among subjects with or without DMARD. Thus, monotherapy is agreed.

The vast majority of subjects tested positive for the HLA-B27 antigen. Thus, although subgroup analyses suggested efficacy also in subjects negative for HLA-B27 antigen, experience in this subgroup is limited.

Dose adjustment across indications
In all three RA studies, there was no improved efficacy with 100 mg golimumab compared with 50 mg, with the possible exception of patients with high body weight. In the AS and PsA studies, nearly 50% of subjects who entered early escape from the placebo group and received golimumab 50 mg, achieved ACR20/ASAS20 after 2 doses, while subjects who entered early escape from the golimumab 50 mg group and received 100 mg did not show substantial improvement. Thus, there is little support for increasing the dose in a subject who does not respond to golimumab within a 14-16 weeks period. However, for subjects with high body weight, an option for a dose increase is warranted, and has been addressed in the SPC.

Risks:

- Demonstrated risks

The safety profile of golimumab appears fully in line with the well known safety profile of anti-TNF agents, although long-term safety data are currently still rather limited. Infections including serious cases were the most common adverse event/serious adverse event, and more subjects on golimumab required antibiotic treatment than those on placebo across indications. There also appeared to be a higher incidence of serious infections among subjects who received oral corticosteroids at baseline together with golimumab, compared with subjects not receiving such baseline treatment. There was also an apparent dose related increase in the incidence of AEs, including serious infections with the golimumab + MTX combinations. Among serious infections, sepsis was more frequently observed following golimumab treatment than placebo. So far, few opportunistic infections have been reported, and seven TB cases have also been reported. There was a relatively high proportion of patients (approx. 14%) who received prophylactic TB treatment. Although data are limited, none of those have so far developed TB.

- Potential risks

The uncertainties related to long-term use of TNF-alpha inhibitors and the potential risk for malignancy are well known concerns associated with the use of TNF-alpha inhibitors. In the placebo controlled phases of the rheumatologic studies, there was an increased incidence of lymphoma in golimumab treated patients, while the incidence of non-melanoma skin cancers and other malignancies was increased in the placebo groups. Additional 52 weeks data have been submitted, showing a similar picture, but the observational time period is still too short to draw definite conclusions.

The findings in the 52 weeks study in severe asthma (no malignancy among placebo subjects (n=78), and 8 cases among 231 golimumab treated subjects) raise serious concern, although the different patient population and the use of higher doses than applied for are acknowledged. The applicant has not been able to establish any obvious explanation for this finding. These results remain a concern and will be further explored within the post-marketing follow-up. The potential risk for malignancy has to be weighed against the potential benefit of golimumab therapy in the indications applied for. Long-term follow up of patients, as well as via registries is of importance.

Across the Phase 3 studies, more patients had vascular disorders when treated with golimumab than placebo. This difference was mostly due to the adverse event hypertension. There was no clear signal for other cardiac disorders. Hypertension, CHF, arrhythmia and ischemic coronary artery disorders are included in the SPC and CHF and hypertension are addressed in the RMP.

Injections reactions were more frequent in golimumab studies, and there was 1 serious injection site reaction, injection site erythema which lead to discontinuation of study agent and 1 non seroius injection site reactions (injection-site erythema) leading to discontinuation. Based on limited data from all Phase 3 studies, a higher proportion of injection-site reactions were observed in subjects who were positive for antibodies to golimumab compared with subjects who were negative or had undetectable antibodies. There is no indication of severe/serious reactions linked to development of antibodies. In addition, so far, there are no concerns identified with respect to anaphylactic reactions and serum sickness.

Regarding autoimmune disorders including antinuclear antibodies/double-stranded DNA antibodies, pulmonary adverse events, CHF, demyelinating disorders or laboratory measurements, there are no findings that raise new concerns regarding the safety profile of an anti-TNF agent. Hepatobiliary adverse events have been analysed in depth by the applicant. Overall, there is no worrying signal in the currently available material. Still, all relevant information is contained in the SPC.

The RMP addresses these risks adequately, and several risk minimisation activities have been implemented. Further long-term data will be provided when available. Protocols for registry follow up as well as a claims database study in the US have been submitted, and are considered to sufficiently cover long-term follow up post marketing.

Balance:
Overall, statistically significant and clinically relevant efficacy on signs and symptoms has been shown across the three indications applied for. With support from newly submitted controlled data from C0524T05, updated safety data, as well as indirect evidence with respect to potential effects on joints, second line indications in RA, PsA and AS can be agreed.

For treatment naïve RA, 52 weeks data on signs and symptoms have been submitted, which show a small additional benefit (6-8%) by adding 50 mg golimumab to MTX. Considering the risks with anti-TNF agents, it is not considered justified to add golimumab to MTX in the treatment of treatment naïve RA without evidence of beneficial effects on structural damage. Thus, the lack of x-ray data for golimumab is still considered a major shortcoming, particularly taking the somewhat unconvincing data for signs and symptoms with the dose applied for, both at week 24 and week 52, into account.

The safety profile is as expected for an anti-TNF agent, although long-term data are lacking. Infections, and risk for malignancy are the main concerns in general. Specifically, the finding of malignancy in the severe asthma study is disturbing, but the considerably larger safety database from the rheumatological indications is sufficiently reassuring, and this finding is not considered to question the approvability of the rheumatologic indications. Nevertheless, adequate information in the product information and follow up are necessary to support a positive benefit /risk balance.

A shortcoming with the dossier is the lack of directly comparative data with other anti-TNF agents.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:
- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see as detailed in the Annex "Conditions or Restrictions with regard to the Safe and Effective Use of the Medicinal Product to be implemented by the Member States"

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Simponi in the following indication:

"Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
Simponi has also been shown to improve physical function in this patient population.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Simponi has also been shown to improve physical function in this patient population.

Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy."

was favourable and therefore recommended the granting of the marketing authorisation.