Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Golimumab (rmc)

Proprietary Product Name: Simponi and Simponi Smartject Injector

Sponsor: Janssen-Cilag Pty Ltd

Date of first round CER: 10 October 2012

Date of second round CER: 2 January 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR-N	American College of Rheumatology-N index of improvement
AE	adverse event
ANOVA	analysis of variance
AS	ankylosing spondylitis
BSA	body surface area
CCP	cyclic citrullinated peptide
CI	confidence interval
CRP	C-reactive protein
CSR	Clinical Study Report
DAS28	Disease Activity Score including evaluation of 28 joints
DAS28 (CRP)	Disease Activity Score including evaluation of 28 joints and CRP
DIP	distal interphalangeal
DMARD	disease-modifying anti-rheumatic drug
EE	early escape
EU	European Union
ECLIA	electrochemiluminescent immunoassay
GI	gastrointestinal
GO	gross osteolysis
HAQ	Health Assessment Questionnaire
Hgb	haemoglobin
ITT	intention to treat
JSN	joint space narrowing
LFT	liver function test

Abbreviation	Meaning
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MASES	Maastricht AS Enthesitis Score
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NAb	neutralizing antibody
NCE	new chemical entity
NND	No new data provided
NSAID	non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PCS	physical component summary
PGA	Physician Global Assessment
PIC	pencil-in-cup (deformity)
PP	per protocol
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QOL	quality of life
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software™
SC	subcutaneous
SD	structural damage

Abbreviation	Meaning
SF-36	36-item short form health survey
SJC	swollen joint count
TB	tuberculosis
TJC	tender joint count
TNFα	tumour necrosis factor alpha
ULN	upper limit of normal
VAS	Visual Analogue Scale
vdH-S	van der Heijde-Sharp (score)
WBC	white blood cell (count)

1. Introduction

The sponsor seeks to extend the indications of SIMPONI by inclusion of inhibition of structural damage under both RA and PsA. There are no proposed changes to the indication for AS. The sponsor also proposes to add information to the *Clinical trials* section of the PI for both RA and PsA.

Substantial long-term efficacy data have been added to *Clinical trials* section to support the additional proposed indications. A safety update relating to the timing of hypersensitivity reactions is also proposed under *Adverse events*.

1.1. Clinical rationale

Chronic rheumatic diseases such as RA are treated with a variety of agents including disease modifying anti-rheumatic drugs (DMARDS) such as methotrexate, local or systemic steroids, NSAIDs and simple analgesics. Several biological DMARDS have been marketed in the last 10 years and used alone or in combination with the traditional therapies. TNFα is an important inflammatory mediator implicated in the pathophysiology of several immune mediated diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). TNF acts on osteoclasts and synovial enzymes resulting in bone erosions and joint space narrowing (JSN), seen particularly in RA patients. Anti-TNF antibodies prevent downstream signalling cascades and limit the damaging effects of excessive TNF expression. Treatment with anti-TNFα agents has been shown to improve the signs, symptoms, physical function and QOL in patients with RA, PsA and AS. Approved anti-TNF agents have also been shown to limit the rate of progression of structural damage in RA and PsA patients (1-7). Golimumab is a human monoclonal antibody which binds with high affinity to both soluble and membrane forms of TNFα. Given SC once monthly, it has been approved for the treatment of RA, PsA and AS.

1.2. Overseas regulatory history

Similar submissions were made in the US, Canada and Europe in 2010. The sponsor received a complete response letter from the FDA in 2011 requesting additional information to support the structural damage (SD) indication. NCE submissions (including the SD indication) have been made in Switzerland, New Zealand and various other countries in Asia, Latin America and North Africa.

1.3. Guidance

A pre-submission planning form for the extended indications was lodged with the TGA in March 2012. Guidance included adoption by the TGA of EMEA/CHMP guidelines for the clinical use of medicinal products for the treatment of RA, PsA and AS; the clinical investigation of medicinal products for long-term use; and the extent of population exposure to assess clinical safety for medicines intended for long-term treatment of non-life-threatening conditions. Clinical endpoints used in the study were those recommended in the relevant EU guideline.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- One clinical pharmacology study to compare the PK/PD of SC versus IV golimumab, and one study to assess the absolute bioavailability of SC golimumab in healthy subjects.
- Three pivotal Phase 3 studies in patients with RA (C0524T05, C0524T06, C0524T12).
- A corrective update on the GO-AFTER study (previously evaluated by the TGA[1]).
- One pivotal Phase 3 study in patients with PsA (C0524T08).
- Additional safety data are included from studies C0524T09 (AS) and C0524T11 (RA, 24 Weeks[2]).
- Literature references

Module 1

- Application letter, application form, draft Australian PI and CMI, and overseas regulatory status.

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and study synopses.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

All studies were conducted according to ICH[3] Good Clinical Practice requirements.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

[1] The evaluators conclusions regarding the correction update report were: "The data corrections applied to DAS28 (using CRP) scores which affected several secondary endpoints. The changes were minor and they did not affect the primary endpoint. Moreover, they did not change the statistical outcome or overall clinical interpretation of the secondary endpoints. Structural damage was not assessed in this study so the conclusions have no direct bearing on the proposed new indication." The evaluator's full review of the correction update is not included in this Extract.
[2] Sponsor clarification: Additional safety data are included from Study C0524T12 (RA 48 weeks).
[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	
PK in healthy adults	General PK Single dose	C0524T15	Absolute bioavailability of golimumab 100 mg SC in healthy subjects
	Multi dose	NND	
	Bioequivalence† Single dose	NND	
	Multi-dose	NDD	
	Food effect	NA	
PK in special populations	Target population §		
	Single dose	NND	
	Multi-dose	C0524T14	PK/PD of 100 mg SC and 2 mg/kg IV golimumab in patients with RA
	Hepatic impairment	NND	
	Renal impairment	NND	
	Neonates/infants/children/ adolescents	NND	
	Elderly	NND	
	Other	NND	
Genetic/ gender-related PK	Males versus females	NND	
	Other	NND	
PK interactions		NND	
Population PK analyses	Healthy subjects	NND	
	Target population	C0524T05 C0524T06 C0524T09 C0524T08 C0524T11	Trough PK for golimumab 50 mg and 100 mg in Phase 3 studies through week 104
	Other	NND	

NND: No new data were provided by the sponsor

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

NND

3.2.1. Bioavailability

3.2.1.1. Absolute bioavailability

The absolute bioavailability of golimumab 100 mg SC was shown to be 51% in the single dose study C0524T15.

3.2.1.2. Bioequivalence of clinical trial and market formulations

NND

3.2.1.3. Bioequivalence of different dosage forms and strengths

NND

3.2.1.4. Bioequivalence to relevant registered products

NND

3.2.1.5. Influence of food

N/A

3.2.1.6. Dose proportionality

NND

3.2.1.7. Bioavailability during multiple-dosing

The bioavailability of golimumab 100 mg SC was 53% in the multiple dose study C0524T14.

3.2.1.8. Effect of administration timing

NND

3.2.2. Distribution

NND

3.2.3. Metabolism

NND

3.2.4. Excretion

NND

3.2.5. Intra- and inter-individual variability of pharmacokinetics

The overall mean bioavailability after SC administration of 100 mg golimumab at three injection sites was 51% with a standard deviation of 15%. The variability of absolute bioavailability (%CV) after SC administration was 29.2% (see *Absolute bioavailability*, above).

3.3. Pharmacokinetics in the target population

PK data were assessed following 100 mg golimumab given SC or IV in patients with RA in the multiple dose study C0524T14. Overall, there were no significant differences between the PK

parameters observed in this study compared with those observed in healthy volunteers. Trough serum golimumab concentrations were measured through Week 100/104 in the Phase 3 studies. Golimumab concentrations were maintained over the treatment period in patients receiving golimumab 50 mg and 100 mg.

3.4. Pharmacokinetics in other special populations

NND

3.5. Pharmacokinetic interactions

NND

4. Evaluator's overall conclusions on pharmacokinetics

The kinetics and bioavailability of golimumab 100 mg SC are similar in patients compared with healthy volunteers and the %CV was acceptable. Bioavailability of the 100 mg SC dose is comparable to the marketed 50 mg dose (if dose linearity was available in previous studies these data should be provided by the sponsor).

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

Table 2. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary Aim of Study
Primary Pharmacology	PK comparison of multiple doses of SC and IV golimumab	C0524T14	PK/PD of 100 mg SC and 2 mg/kg IV golimumab in patients with RA
	Effect on serum biomarkers	C0524T14	
Secondary Pharmacology	Effect on clinical efficacy	C0524T14	
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	NND	
	Effect of age	NND	
PD Interactions		NND	
Population PD and PK-PD analyses	Healthy subjects	NND	
	Target population	NND	

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.3. Mechanism of action

NND

5.4. Pharmacodynamic effects

5.4.1. Primary pharmacodynamic effects

NND

5.4.2. Secondary pharmacodynamic effects

NND

5.5. Time course of pharmacodynamic effects

NND

5.6. Relationship between drug concentration and pharmacodynamic effects

NND

5.7. Genetic-, gender- and age-related differences in pharmacodynamic response

NND

5.8. Pharmacodynamic interactions

NND

5.9. Evaluator's overall conclusions on pharmacodynamics

One new study examined the effects of multiple doses of golimumab 100 mg SC given once monthly on PK/PD in patients with RA. PD endpoints included multiple serum biomarkers and clinical indices. There were meaningful improvements in several clinical measures including joint inflammation and function. However, there were less marked and inconsistent changes in serum biomarkers which did not correlate with improved clinical outcomes. Steady state serum concentrations of golimumab were achieved following once monthly 100 mg SC injections but they were not achieved with q12 week 100 mg[4] IV dosing. The study did not test the 50 mg SC once monthly regimen used in the Phase 3 studies.

[4] Erratum: correct dose is 2 mg/kg IV

6. Dosage selection for the pivotal studies

NND

7. Clinical efficacy

7.1. Pivotal efficacy studies

7.1.1. Active psoriatic arthritis

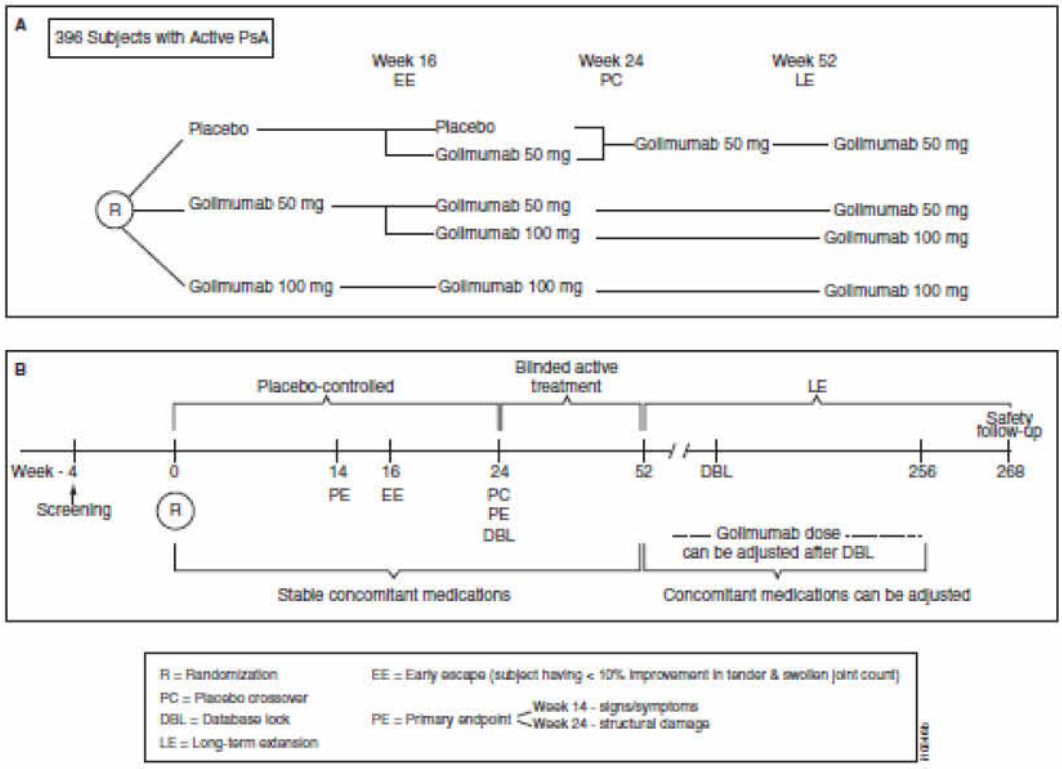
7.1.1.1. Study C0524T08 (GO-REVEAL)

7.1.1.1.1. Study design, objectives, locations and dates

This is an on-going multicentre, randomized, double-blind, placebo-controlled Phase 3 trial of golimumab in adult patients with active psoriatic arthritis. The study was designed to compare the efficacy, safety and clinical pharmacology of golimumab 50 mg or 100 mg given SC once monthly. Patients were randomly assigned and stratified according to concomitant MTX use. At Week 16, patients who had <10% improvement in tender or swollen joint count from baseline in any treatment group were entered into a double blind treatment group dosed with golimumab 50 mg or 100 mg SC (EE, early escape). At Week 24, patients in the placebo group were switched double-blind to receive golimumab 50 mg SC every 4 weeks, while patients already in the golimumab groups remained on their randomized treatment. From Weeks 24 to 52, all patients were receiving golimumab although the doses (50 mg or 100 mg) remained blinded. The blinded study was completed at Week 52 following database lock and the remaining patients were enrolled into an on-going, open-label, long-term extension study (LTE). At Week 52, patients receiving golimumab 50 mg SC were allowed to increase the dose to 100 mg at the discretion of the investigator. Patients already receiving golimumab 100 mg SC every 4 weeks remained on that dose. The open-label extension study will be completed when the last patient completes Week 268. The present interim analysis has been conducted at the Week 104 time-point. The study up to Week 104 was conducted between December 2005 and 2008 at 58 centres (36 sites in N. America and 22 sites in Europe).

Radiographic assessment of structural damage was based on X-rays of hands and feet using the van der Heijde-Sharpe (vdH-S) score which includes 40 joints in the hands and 12 joints in the feet scored for erosions and JSN. Higher/lower scores indicate greater/lesser degrees of structural damage. Initial radiographic reporting included images from baseline, Week 24 and Week 52, followed by separate reporting of the Week 104 images. The scores from the two readings were analysed and reported separately but the reviewing radiologists were the same. A random sample of patients was selected and the images were reread to assess intra-reader variability, and the scores were used for intra-class correlation analysis. A range of data handling rules and sensitivity analyses were applied to allow for missing assessments, patient withdrawals and early escape changes to randomised therapies. The study schema is shown below:

Figure 1. Study C0524T08 (GO-REVEAL) schema



Panel A shows study treatments; Panel B shows key time points during the study.

The primary objectives of the study were:

- Reduction in signs and symptoms of PsA
- Inhibition of progression of structural damage

The secondary objectives were:

- Achievement of sustained arthritic response
- Improvement of psoriatic skin lesions
- Improved physical function
- Improved quality of life
- Safety

7.1.1.1.2. Inclusion and exclusion criteria

Male and female patients aged 18 years or older with active PsA despite current or previous DMARD or NSAID therapy were eligible. Exclusion criteria included prior exposure to anti-TNFα therapy.

7.1.1.1.3. Study treatments

From Week 52 onwards, patients received SC injections every 4 weeks via pre-filled syringes containing golimumab 50 mg or 100 mg in an aqueous medium. After the first visit, injections were allowed to be self-administered or given by a trained relative or care giver.

7.1.1.1.4. Efficacy variables and outcomes

The co-primary efficacy outcomes were:

- Change from baseline to Week 24 in the proportion of patients with radiographic progression (erosions and JSN) assessed by modified vdH-S score
- The proportion of patients with ACR 20 response at Week 14

Other efficacy outcomes included:

- DAS-28 (CRP) score
- Change from baseline to Weeks 52 and 104 in vdH-S score.
- ACR 50 and 70 responses after Weeks 52 and 104, with adjustment for MTX use.
- The proportion of patients who achieved PASI 50, 75, and 90 responses by Week 104.
- Change from baseline to Week 104 in SF-36 quality of life and HAQ scores.

7.1.1.1.5. Randomisation and blinding methods

These are described in the Week 24 CSR which is not included in the current submission.

7.1.1.1.6. Analysis populations

The radiographic data were summarised by randomised treatment groups: placebo, golimumab 50 mg and golimumab 100 mg. For selected radiographic and other efficacy data, the following treatment groups were described: placebo to golimumab 50 mg; golimumab 50 mg only; golimumab 50 mg to golimumab 100 mg; and golimumab 100 mg only.

7.1.1.1.7. Sample size

Power, sample size and Type 1 error are described in the Week 24 CSR which is not included in the current submission.

7.1.1.1.8. Statistical methods

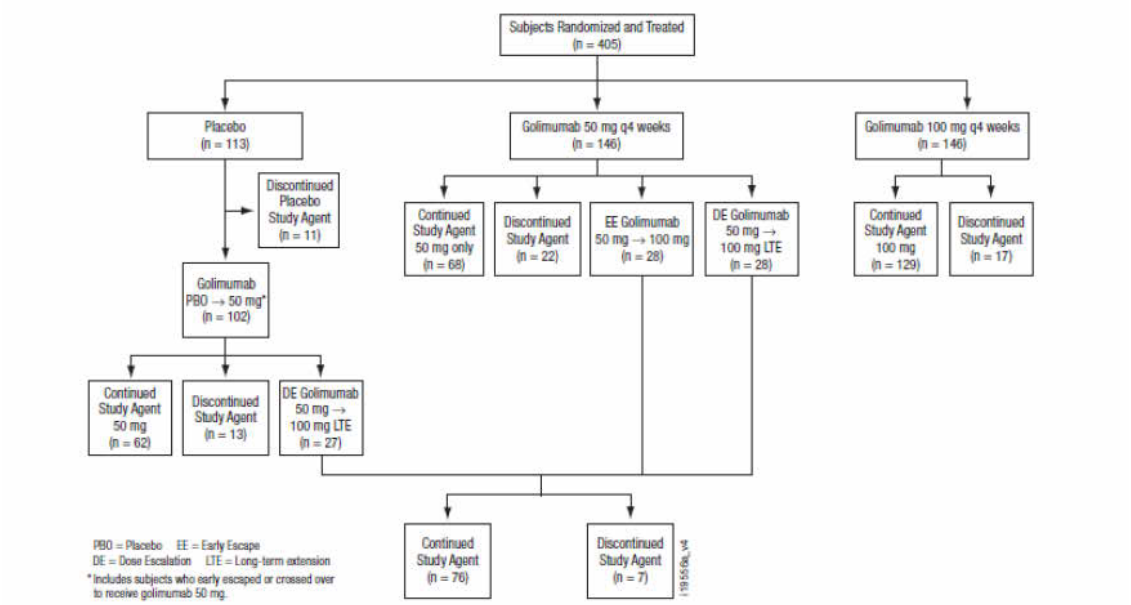
Descriptive statistics were used to summarise most data. No statistical comparisons with p-values were made due to the lack of a placebo control arm.[5]

7.1.1.1.9. Participant flow

A total of 405 patients were randomised to treatment as shown in Figure 2 below. Approximately 17% of patients discontinued their randomised treatment before Week 104. Overall, 6.7% of patients were withdrawn because of AEs (8.0% in the placebo group) and 3.7% withdrew because of an unsatisfactory therapeutic effect. No patients were withdrawn because of an AE worsening of psoriatic arthritis.

[5] Sponsor clarification: This sentence should read: *No statistical comparisons with p-values were made after Week 24 due to the lack of a placebo control arm.*

Figure 2. Study C0524T08 (GO-REVEAL) participant flow. Subject disposition at Week 104; randomised subjects.



7.1.1.1.10. Major protocol violations/deviations

Approximately 25% of patients missed one or more doses of golimumab during the course of the study. The number of missed doses was similar in all treatment groups. There were no other major deviations during the 104 week treatment period.

7.1.1.1.11. Baseline data

Baseline demographics were well balanced across the treatment groups. Most patients were male (60.2%) and White (97.0%) with a median age of 47.0 years. The baseline disease characteristics were also similar across the treatment groups. Overall, the median duration of psoriasis was approximately 17 years and the median duration of PsA was approximately 5 years. Approximately half the patients were receiving MTX at baseline.

7.1.1.1.12. Results for the primary efficacy outcome

The majority of patients had X-ray images and radiographic scores at baseline (approximately 98%), at Week 52 (approximately 91%) and at Week 104 (approximately 84%). The changes from baseline in total modified vdH-S scores at Week 104 for each treatment group are shown in Table 3.

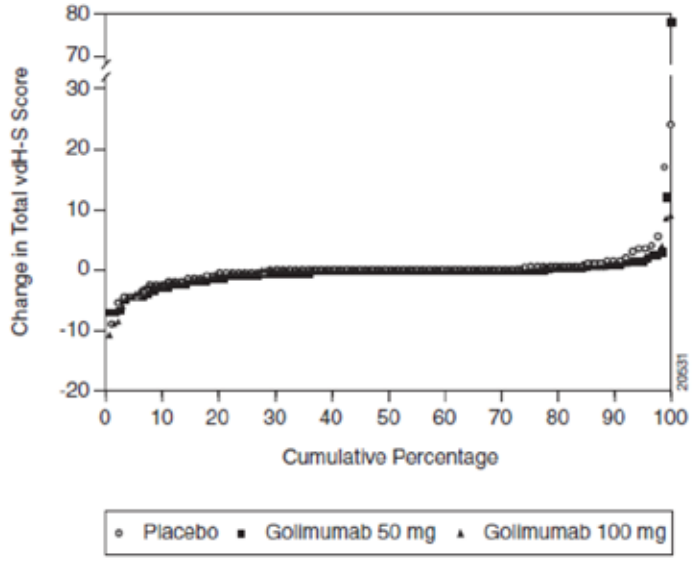
Table 3. Study C0524T08. Summary of change from baseline in total modified van der Heijde Sharp score at Week 52 and Week 104 (with imputation rules applied to all timepoints); randomized subjects (Reading session 2)

		Golimumab		
	Placebo[a]	50 mg[b]	100 mg	Combined
Change from baseline at Week 52[d]				
n	89	119	130	249
Mean ± SD	0.25 ± 2.621	0.28 ± 7.450	-0.37 ± 2.079	-0.06 ± 5.363
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(-0.50, 0.00)	(0.00, 0.00)	(-0.50, 0.00)
Range	(-5.0, 17.0)	(-7.0, 78.6)	(-11.0, 8.5)	(-11.0, 78.6)
Change from baseline at Week 104[d]				
n	89	120	130	250
Mean ± SD	0.22 ± 3.666	0.19 ± 7.471	-0.33 ± 2.229	-0.08 ± 5.415
Median	0.00	0.00	0.00	0.00
IQ range	(-0.50, 0.50)	(-1.00, 0.00)	(-0.50, 0.00)	(-0.50, 0.00)
Range	(-9.0, 24.0)	(-7.0, 78.0)	(-10.8, 9.0)	(-10.8, 78.0)

[a] Includes subjects who early escaped at Week 16 or crossed over at Week 24 to receive golimumab 50 mg or dose escalated after Week 52 database lock to receive golimumab 100 mg.
[b] Includes subjects who early escaped at Week 16 or dose escalated after Week 52 database lock to receive golimumab 100 mg.
[c] Includes subjects who had at least one total modified vdH-S score post Week 52.
[d] Missing imputation rules were applied.

A pre-determined sensitivity analysis was applied, analysing only patients who had baseline scores and at least one score after week 52. The findings in the sensitivity analysis were similar to the primary analysis with the exception of the golimumab 50 mg group. In the sensitivity analysis (per protocol), but not the primary analysis (ITT), there was a negative mean change in total modified vdH-S score in the golimumab 50 mg group at both Week 52 and Week 104. Radiographic progression scores are shown graphically in Figure 3.

Figure 3. Study C0524T08. Empirical cumulative distribution function of change from baseline in total modified vdH-Score at Week 104 (missing imputation rules same as Week 104 analysis)



More radiographic progression was noted in patients initially randomised to placebo but approximately 80% of patients across all groups had no radiological progression.

Approximately 20% of patients across treatment groups had a negative change in vdH-S score indicating improved radiographic scores.

The co-primary endpoint was the ACR 20 response at Week 14. The proportion of patients who achieved an ACR 20 response at Week 14 was significantly greater (p<0.001) in the combined golimumab group (47.9%), the golimumab 50 mg group (50.7%) and the golimumab 100 mg group (45.2%), compared with the placebo group (8.8%).

7.1.1.1.13. Results for other efficacy outcomes

The proportions of patients who achieved ACR 20, ACR 50 and ACR 70 responses after Week 52 through Week 104 are provided. Of the 70 patients still receiving golimumab 50 mg at Week 104, 91.4%, 65.7% and 44.3% patients respectively achieved ACR 20, 50 and 70 responses. Overall, the proportion of patients who achieved an ACR response at Week 14 was maintained up to Week 104. The median percent improvement from baseline in swollen and tender joint counts was similar after Week 52 through Week 104 in each treatment group. At Week 104, the median improvement from baseline in the number of swollen joints was between 84.25% and 100%. The median percent improvement from baseline in the number of tender joints was between 80% and 100%. The proportion of patients with a DAS28 (CRP) response was maintained after Week 52 through Week 104 in all treatment groups. At Week 104, the proportion of patients with a DAS28 (CRP) response was between 84.7% and 100% across the treatment groups. The proportion of patients with PASI response was maintained after Week 52 through Week 104 in each treatment group. Overall, approximately 50% of patients achieved a PASI 90 response. Between 86.8% and 100% of patients who achieved an improvement in HAQ score at Week 52 maintained the improvement at Week 104. Health related quality of life was measured by the 36-Item Short Form Health Survey (SF-36). The proportion of patients with improved QOL at Week 52 was maintained at Week 104.

7.1.2. Rheumatoid arthritis

7.1.2.1. Study C0524T05 (GO-BEFORE)

7.1.2.1.1. Study design, objectives, locations and dates

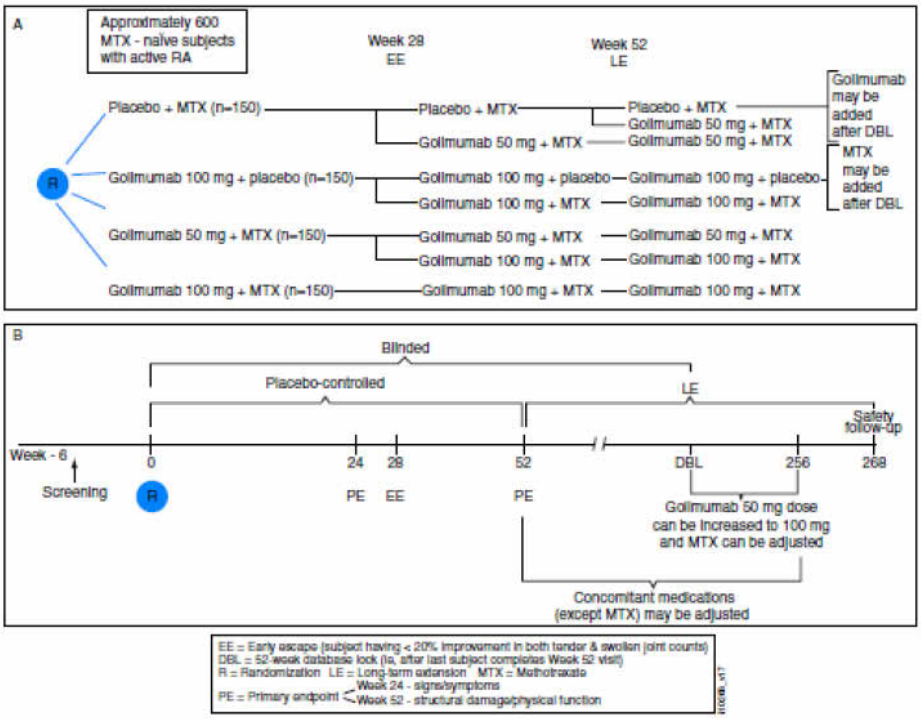
This is an ongoing Phase 3, multi-centre, randomised, double-blind, placebo-controlled, 4-arm trial of SC golimumab in MTX-naive patients with active RA. The study was conducted between December 2005 and May 2009. There were 90 sites: 25 sites in Asia, 34 sites in Europe/Australia/ New Zealand, 10 sites in Latin America, and 21 sites in N. America.

Patients were randomised to receive golimumab 50 mg or 100 mg or placebo SC injections at Week 0 and every 4 weeks thereafter through Week 48. At Week 28, patients with <20% improvement from baseline in swollen and tender joint counts entered early escape (EE) in a double-blind manner. A stable dose of MTX or matching placebo was to be given with the SC injections. The blind was maintained until the last subject completed the Week 52 evaluation and the database was locked. Visits were scheduled at 4 week intervals until Week 64 and then every 12 weeks until approximately 5 years of follow-up. The study will continue through Week 256 and this evaluation assesses the Week 104 data. The study schema is shown below in Figure 4.

The co-primary objectives were to demonstrate reduction of signs and symptoms of RA at Week 24, and inhibition of progression of structural damage at Week 52. The secondary objectives were to assess safety, physical function, health-related QOL and population PK in MTX-naive patients with active RA. Progression of structural damage was assessed by conventional radiographs. In addition, MRI assessments were planned for approximately 300 patients based on the availability of MRI at the selected sites. Two independent, blinded readers reported the images, and a random sample of images was reread to assess intra-reader variability. The reread scores were used for intra-class correlation analysis. Data handling rules and sensitivity

analyses were applied to allow for missing assessments, patient withdrawals and early escape changes to randomised therapies.

Figure 4. Study C0524T05 (GO-BEFORE) schema



Study schema
Panel A shows study treatments; Panel B shows key time points during the study.

7.1.2.1.2. Inclusion and exclusion criteria

Men and women aged 18 years or older were eligible if they had active RA for at least 3 months and had not received MTX therapy. Key exclusion criteria included patients with active or latent TB, other significant infections, other significant inflammatory disease, and previous anti-TNFα therapy or DMARDs.[6]

7.1.2.1.3. Study treatments

The study treatments during the LTE from Week 52 through Week 252 are:

- Group 1: Placebo + MTX capsules.
- Group 2: Golimumab 100 mg SC injections + placebo capsules
- Group 3: Golimumab 50 mg SC injections + MTX capsules
- Group 4: Golimumab 100 mg SC injections + MTX capsules

The first dose of study treatment was administered by qualified site staff. Thereafter, self-injection or injections given by a family member were permitted. Overall, 52.8% of patients self-injected and 21.1% of all doses were self-injected.

[6] Sponsor clarification: This sentence should read: *"Key exclusion criteria included patients with active or latent TB, other significant infections, other significant inflammatory disease, and previous anti-TNFα therapy or with other DMARDs within 4 weeks of study dose"*

7.1.2.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Swollen and tender joint count (ACR 50) at Week 24
- Inhibition of radiographic progression at Week 52

The primary efficacy outcome was inhibition of radiographic progression at Week 104.

Other efficacy outcomes included:

- DAS28 scores
- Disability index of the HAQ
- SF-36 health survey
- CRP and ESR

Note: The radiographic report at Week 104 was not a pre-defined endpoint but *ipso facto* it is the main criterion to support the new proposed indication.

7.1.2.1.5. Randomisation and blinding methods

The blind was to be maintained until after the Week 52 database lock. At this point, at the next study visit and at the discretion of the investigator, patients who were receiving MTX alone were eligible to receive golimumab 50 mg + MTX. Patients who were receiving golimumab 50 mg + MTX were eligible to receive golimumab 100 mg + MTX.

7.1.2.1.6. Analysis populations

Statistical summaries were generated for the following treatment groups:

Group 1: Placebo + MTX → Golimumab 50 mg + MTX (EE patients)

Group 2: Golimumab 100 mg + placebo →Golimumab 100 mg + MTX (EE patients)

Group 3: Golimumab 50 mg + MTX (patients who did not meet EE criteria)

Group 4: Golimumab 50 mg + MTX →Golimumab 100 mg + MTX (EE patients)

Group 5: Golimumab 100 mg + MTX (patients randomised to this treatment regime)

7.1.2.1.7. Sample size

Approximately 600 patients were to be enrolled at approximately 86 global sites.

7.1.2.1.8. Statistical methods

Descriptive statistics were used to summarise most data after Week 52 through Week 104. No statistical comparisons with p-values were made due to the lack of a control arm.

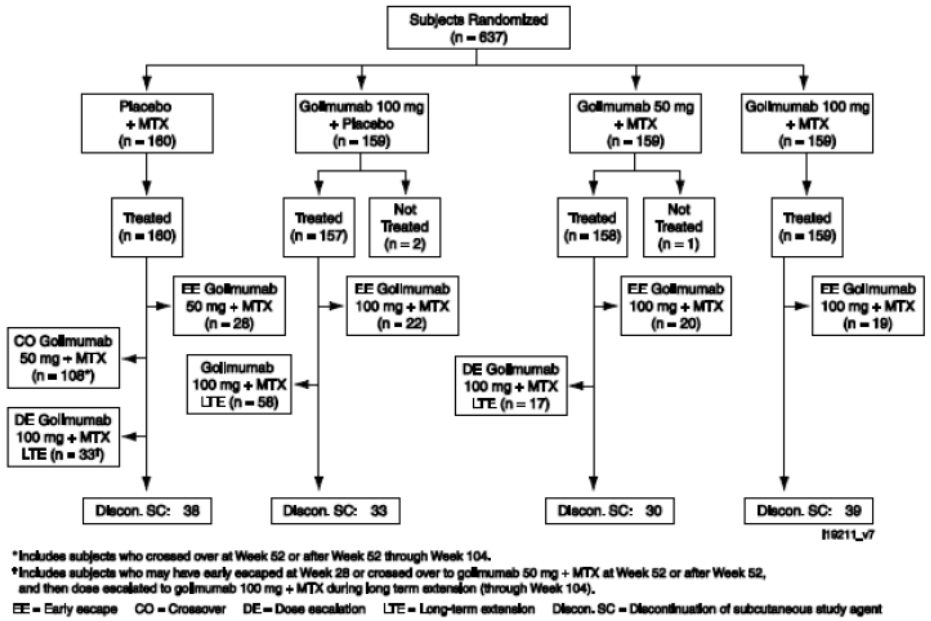
The analysis plan called for radiographic assessment of structural damage to be assessed at Weeks 52 and 104. However, the analysis population was changed *a priori* to those who had a vdH-S score at Week 52 and at least one vdH-S score after Week 52. This modification was required to avoid potential bias due to early withdrawals. The change from baseline in vdH-S score was summarised at Week 104 and a sensitivity analysis was performed to allow for missing scores. A patient with a missing baseline score was excluded from this analysis.

7.1.2.1.9. Participant flow

A total of 637 patients were randomised and 634 patients received at least one dose of study drug as shown below in Figure 5. Approximately 160 patients were randomised and treated in each group. Through Week 104, 140 (22.0%) randomised patients discontinued study treatment**.** The main reason for discontinuation was AEs which occurred in 11.5% of patients

overall. Withdrawal due to unsatisfactory therapeutic response occurred in 2.2% of patients overall.

Figure 5. Study C0524T05 (GO-BEFORE). Participant flow. Study disposition at Week 104; randomized patients.



7.1.2.1.10. Major protocol violations/deviations

There were no patient eligibility violations during the Week 52 to Week 104 period. Protocol deviations related to study treatment administration from Week 52 through Week 104 ranged from 20.0% to 38.8% across treatment groups. Missed treatment administrations due to AEs were permitted in the protocol. Most significant protocol deviations were due to a missed administration of study treatment. However, the great majority of patients who missed a dose missed only one of the scheduled 13 doses (data not shown). A total of 19 patients received an incorrect dose of study treatment. No critical deviations were noted from Week 52 through Week 104.

7.1.2.1.11. Baseline data

Demographics were well balanced across treatment groups. Overall, most patients were female (82.9%), 72.4% were Caucasian and 18.4% were Asian. Median age was 50.0 years and median weight was 69.0 kg. The clinical disease characteristics at baseline were similar and concomitant medications were similar across treatment groups at baseline. From Week 52 through Week 104, the median dose of corticosteroids remained the same, the median dose of MTX decreased and the proportion of patients taking NSAIDs decreased slightly. A greater number of patients reduced rather than increased their dose of oral steroids or DMARDs.

7.1.2.1.12. Results for the primary efficacy outcome

The proportion of patients who achieved an ACR 50 response at Week 24 was greater in the combined golimumab +MTX group (38.4%) than in the placebo + MTX group (29.4%) although the difference was not statistically significant (p=0.053). However, more patients in the golimumab 50 mg + MTX group (40.3%) achieved an ACR 50 response compared with the placebo + MTX group (29.4%, p=0.042). The proportion of patients who achieved ACR 20, 50 and 70 responses from Week 52 through Week 104 is shown in Table 4. In the golimumab + MTX groups, ACR response rates achieved at Week 52 were maintained through Week 104.

Table 4. Number of subjects who achieved ACR 20, ARC 50 and ARC 70 responses after Week 52 through Week 104; randomized subjects who received golimumab + MTX

	Placebo + MTX → Golimumab 50 mg + MTX[a]	Golimumab 100 mg + Placebo → Golimumab 100 mg + MTX	Golimumab + MTX		
			50 mg	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab + MTX[b]	120	22	122	18	137
Subjects in response[c]					
Week 64					
ACR 20	71.9% (82/114)	54.5% (12/22)	87.5% (105/120)	65.2% (15/23)	81.7% (107/131)
ACR 50	48.7% (56/115)	36.4% (8/22)	68.1% (81/119)	8.7% (2/23)	57.3% (75/131)
ACR 70	34.8% (40/115)	22.7% (5/22)	45.4% (54/119)	0.0% (0/23)	34.1% (45/132)
Week 76					
ACR 20	86.8% (92/106)	61.9% (13/21)	85.2% (98/115)	66.7% (20/30)	81.5% (106/130)
ACR 50	61.3% (65/106)	28.6% (6/21)	69.6% (80/115)	16.7% (5/30)	60.0% (78/130)
ACR 70	37.7% (40/106)	14.3% (3/21)	50.9% (58/114)	6.7% (2/30)	37.4% (49/131)
Week 88					
ACR 20	74.5% (76/102)	57.1% (12/21)	87.9% (94/107)	71.4% (25/35)	80.3% (102/127)
ACR 50	49.5% (50/101)	33.3% (7/21)	75.5% (80/106)	42.9% (15/35)	61.4% (78/127)
ACR 70	35.3% (36/102)	14.3% (3/21)	50.0% (53/106)	20.0% (7/35)	46.1% (59/128)
Week 100					
ACR 20	77.3% (68/88)	57.1% (12/21)	85.4% (88/103)	75.0% (36/48)	79.4% (100/126)
ACR 50	62.5% (55/88)	38.1% (8/21)	74.8% (77/103)	50.0% (24/48)	65.1% (82/126)
ACR 70	38.6% (34/88)	28.6% (6/21)	51.0% (52/102)	20.8% (10/48)	42.1% (53/126)
Week 104					
ACR 20	84.0% (63/75)	61.9% (13/21)	88.5% (85/96)	81.5% (53/65)	82.1% (101/123)
ACR 50	62.7% (47/75)	33.3% (7/21)	69.5% (66/95)	50.8% (33/65)	61.6% (77/125)
ACR 70	43.2% (32/74)	20.0% (4/20)	55.8% (53/95)	24.6% (16/65)	45.5% (56/123)

[a] This group includes subjects randomized to placebo + MTX who early escaped at Week 28 or crossed over at Week 52 to 50 mg + MTX through the last visit on 50 mg + MTX.
[b] By assigned treatment group as of Week 52.
[c] Subjects are counted in the column through the last visit on that dose.

The majority of patients had a radiographic image and score at baseline (approximately 99%), at Week 52 (approximately 88%) and at Week 104 (80%). The decrease in radiographic images and scores between Weeks 52 and 104 was due mainly to patient discontinuations. At baseline, vdH-S scores were generally similar across all treatment groups. At Week 52, the combined golimumab 50 mg + MTX and golimumab 100 mg + MTX groups were superior to placebo in inhibition of radiographic progression assessed by vdH-S scores (p=0.006). The golimumab 50 mg + MTX and golimumab 100 mg + MTX groups were also significantly superior to the placebo + MTX group (p=0.015 and p=0.025 respectively). The mean change from baseline values at Week 52 and Week 104 is shown in Table 5.

Table 5. Study C0524T05. Summary of change from baseline in total van der Heijde modified Sharpe score at Week 52 and Week 104 (with imputation rules applied to all timepoints) stratified by screening CRP level; randomized subjects (Reading session 2)

	Placebo + MTX[a]	Golimumab 100 mg + Placebo[b]	Golimumab + MTX		
			50 mg[c]	100 mg	Combined
Randomized subjects (Reading Session 2)[d]	131	128	133	127	260
Change from baseline to Week 52[e]					
n	129	128	133	126	259
Mean ± SD	0.80 ± 3.160	1.21 ± 6.110	0.06 ± 1.725	0.01 ± 1.362	0.03 ± 1.556
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(0.00, 1.00)	(0.00, 0.50)	(-0.50, 0.50)	(-0.50, 0.50)
Range	(-8.0, 19.0)	(-8.5, 59.5)	(-8.0, 11.5)	(-9.5, 6.5)	(-9.5, 11.5)
Subjects with CRP < 1.5 mg/dL at screening					
n	60	67	68	62	130
Mean ± SD	0.65 ± 2.298	-0.04 ± 1.435	-0.04 ± 1.117	0.17 ± 0.614	0.06 ± 0.915
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(-0.25, 0.50)	(-0.50, 0.50)	(0.00, 0.00)	(0.00, 0.50)	(0.00, 0.50)
Range	(-1.5, 15.5)	(-8.5, 3.5)	(-3.0, 5.5)	(-1.5, 2.0)	(-3.0, 5.5)
Subjects with CRP ≥ 1.5 mg/dL at screening					
n	69	61	65	64	129
Mean ± SD	0.93 ± 3.765	2.59 ± 8.549	0.15 ± 2.193	-0.15 ± 1.808	0.00 ± 2.009
Median	0.00	0.50	0.00	0.00	0.00
IQ range	(0.00, 1.00)	(0.00, 1.50)	(-0.50, 0.50)	(-0.50, 0.50)	(-0.50, 0.50)
Range	(-8.0, 19.0)	(-3.5, 59.5)	(-8.0, 11.5)	(-9.5, 6.5)	(-9.5, 11.5)
Change from baseline to Week 104[e]					
n	131	128	133	127	260
Mean ± SD	0.94 ± 4.237	2.54 ± 13.736	-0.03 ± 1.927	-0.20 ± 1.983	-0.11 ± 1.953
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(0.00, 1.00)	(-0.50, 0.50)	(-0.50, 0.50)	(-0.50, 0.50)
Range	(-14.0, 23.3)	(-9.0, 133.5)	(-8.5, 12.0)	(-12.5, 6.5)	(-12.5, 12.0)

Overall, the reductions from baseline to Week 52 in total vdH-S scores for the golimumab + MTX groups were minor compared with the golimumab + placebo and placebo + MTX treatment groups. At Week 104, the mean change from baseline in total vdH-S score for the placebo + MTX group was higher than in the golimumab + MTX groups, but similar to the placebo + MTX score at Week 52. The results indicate that the change in vdH-S scores between the placebo + MTX group and the golimumab + MTX groups was driven by changes in the first 52 weeks. Apparent worsening of vdH-S scores in the golimumab 100 mg + placebo and CRP <1.5 was due to applied missing data imputation rules for one subject with a missing baseline total modified vdH-S score.

7.1.2.1.13. Results for other efficacy outcomes

Median improvements in ACR-N and CRP in the golimumab groups were maintained after Week 52 through Week 104. The number of DAS28 (including CRP) responders at Week 104 is shown in the CSR. Overall, the DAS28 responses achieved at Week 52 were maintained at Week 104 in all treatment groups. Patients randomised to golimumab 50 mg + MTX or golimumab 100 mg + MTX had comparable DAS28 scores at Week 52 and Week 104. Improvement in physical function as measured by change in HAQ score at Week 52 was comparable at Week 104. Health related quality of life was measured by change in SF-36. Improvements observed in the golimumab + MTX groups were maintained at Week 104.

7.1.2.2. Study C0524T06 (GO-FORWARD)

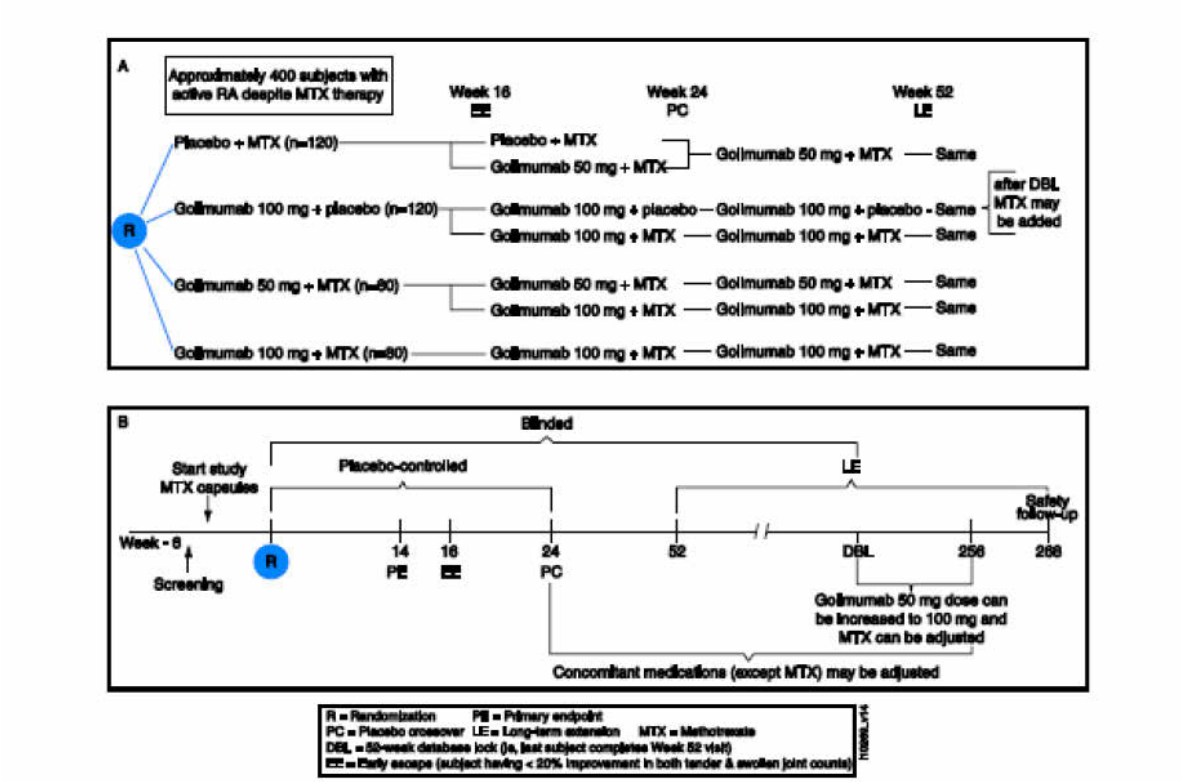
7.1.2.2.1. Study design, objectives, locations and dates

This is an on-going Phase 3, multicentre, randomised, double-blind, placebo-controlled, safety and efficacy study of golimumab 50 mg + MTX or 100 mg + MTX compared with placebo + MTX in patients with active rheumatoid arthritis despite methotrexate therapy. Patients received SC injections at baseline and thereafter every 4 weeks through Week 48. With the exception of the 100 mg + MTX group, treatments were escalated at Week 16 in patients with inadequate response. At Week 24, all patients receiving placebo + MTX were switched to SC golimumab 50 mg + MTX and followed through Week 52 to Week 104. The study will be completed when the last patient completes Week 268 and this evaluation reviews data to Week 104. The first study drug administration was performed at the study site.

The primary objective of the study was to assess the efficacy of golimumab as measured by the reduction of the signs and symptoms of RA at Week 14 and the improvement in physical function at Week 24. The secondary objectives included the safety of golimumab, the effects of golimumab on structural damage, health-related quality of life and the population PK of golimumab in patients with active RA. The main efficacy objectives of the long-term extension study (LTE), were the effects of golimumab on ACR 20 response, and on structural damage at Week 104 (evaluated here). Radiographic data were reviewed by a central adjudication panel whose members were blind to the randomised treatment. X-ray, MRI imaging and independent radiology readers were provided by BioClinica (Newtown, PA, US) and Perceptive Informatics (Waltham, MA, US). Only after all images were read and adjudicated were the data transferred to the central data management group.

The study was conducted at 65 sites in 12 countries in N America, S. America, Europe, S. Korea, Taiwan, Australia and New Zealand. The study schema is shown in Figure 6 below.

Figure 6. Study C0524T06 (GO-FORWARD) schema



Panel A shows study treatments; Panel B shows key time points during the study.

7.1.2.2.2. Inclusion and exclusion criteria

Key inclusion criteria were men and women aged 18 years or older with a history of active RA despite MTX therapy of at least 15 mg/week and ≤25 mg/week. Key exclusion criteria included other inflammatory diseases; previous treatment with anti-TNFα therapy; treatment with other DMARDs or steroids within 4 weeks of starting the first dose of study drug; recent severe infections; and active or latent TB.

7.1.2.2.3. Study treatments

Golimumab 50 mg or 100 mg or matching placebo was supplied as SC injections. MTX or matching placebo was supplied as oral capsules. The first dose of study treatment was administered by qualified site staff. Thereafter, self-injection or injections given by a family member were permitted. Overall, 66.4% of patients self-injected and 34.5% of all doses were self-injected.

7.1.2.2.4. Efficacy variables and outcomes

The co-primary efficacy variables for the study were:

- The proportion of patients who achieved an ACR 20 response at Week 14.
- HAQ score improvement from baseline to Week 24.

Other efficacy outcomes included:

- Other measures of improvement in RA, physical function and QOL through Week 24.
- Improvement in radiographic imaging data at Week 52 and Week 104.
- Swollen and tender joint count at Week 104.
- Pain assessment.

- Patient and physician global assessments.
- PK assessments and anti-golimumab antibodies.

7.1.2.2.5. Randomisation and blinding methods

Treatment allocation and blinding are described in the Week 24 CSR which is not included in the data submitted in this application. Initial study blinding was conducted by IVRS. The Week 24 and Week 52 databases were locked and unblinded while the patients were still being followed in the long-term extension study. After the Week 52 database lock and at investigator discretion, patients who were receiving golimumab 50 mg had the option to increase the golimumab dose to 100 mg every four weeks.

7.1.2.2.6. Analysis populations

The primary efficacy analyses were performed on all patients randomised at Week 0. This was performed on an ITT basis whether or not they received randomised treatment.

7.1.2.2.7. Sample size

A total of 444 patients who completed Week 52 continued into the LTE.[7]

7.1.2.2.8. Statistical methods

The Week 104 long-term efficacy data were summarised for each of the following groups:

- Placebo + MTX →golimumab 50 mg + MTX
- Golimumab 100 mg + placebo →golimumab 100 mg + MTX
- Golimumab 50 mg + MTX only
- Golimumab 50 mg + MTX →golimumab 100 mg + MTX

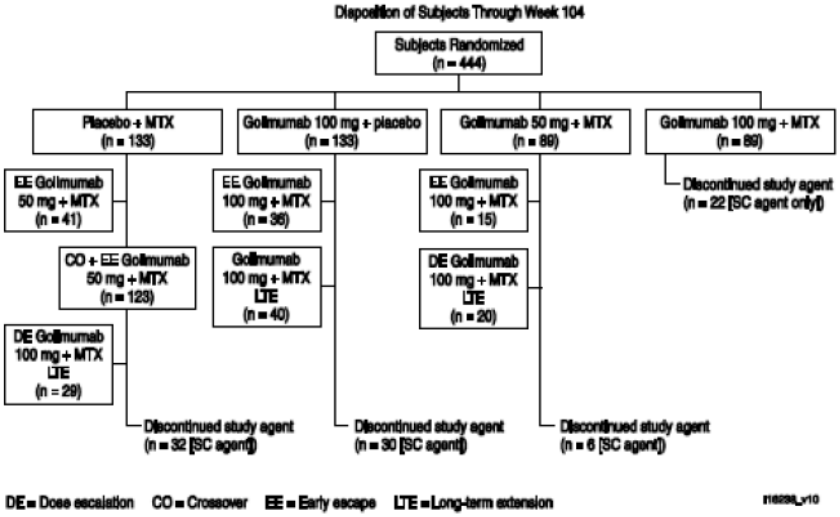
Descriptive statistics were used to summarize most data.

7.1.2.2.9. Participant flow

Of the 444 randomised patients at Week 0, 133 were assigned to placebo + MTX, 133 to golimumab 100 mg + placebo, 89 to golimumab 50 mg + MTX, and 89 to golimumab 100 mg + MTX, as shown below in Figure 7. There were 90 (20.3%) patient discontinuations but the majority received the expected number of doses of golimumab from Week 52 through Week 104. Of patients eligible to receive a dose escalation, approximately 30% were given a dose escalation at the discretion of the investigator. In the combined golimumab + MTX group, 8.4% of patients discontinued study treatment because of AEs and 3.4% discontinued because of inadequate therapeutic effect. A total of 79.7% of patients continued study participation and received study agent to Week 104. The main reason patients discontinued participation in the study was withdrawal of consent.

[7] Sponsor clarification: This sentence should read: *"A total of 444 patients were randomised and those who completed Week 52 continued into the LTE"*

Figure 7. Study C0524T06 (GO-FORWARD). Subject distribution and disposition through Week 104; randomized subjects.



7.1.2.2.10. Major protocol violations/deviations

From Week 52 through Week 104, protocol deviations related to incorrect study drug administration occurred with similar frequency in all treatment groups (range 20.0% to 30.3%). The majority of deviations were due to missed doses. Fourteen patients received an incorrect dose of study agent but none received an incorrect study agent. No other critical deviations were noted between Week 52 and Week 104.

7.1.2.2.11. Baseline data

The demographic characteristics were similar in all treatment groups. The majority were female (80.6%) and Caucasian (76.8%); median age was 51.0 years and median weight was 70.2 Kg. The majority of patients had long-standing moderate to severe disease and baseline disease characteristics were similar in all groups. The proportion of patients who took RA medications prior to study drug administration was similar across treatment groups. Of the 444 patients who received study agent, 295 (66.4%) patients self-administered study drug at least once. A total of 18849 injections were administered through Week 104 and 6496 (34.46%) of these were self-administered.

7.1.2.2.12. Results for the co-primary efficacy outcomes

Overall, the proportion of patients who had an ACR 20, ACR 50 or ACR 70 response was maintained from Week 52 through Week 104 (Table 6).

Table 6. Study C0524T06. Number of subjects who achieved ACR 20, ARC 50 and ARC 70 responses after Week 52 through Week 104; randomized subjects who received golimumab + MTX

	Placebo + MTX → Golimumab 50 mg + MTX[a]	Golimumab 100 mg + Placebo → Golimumab 100 mg + MTX	Golimumab + MTX		
			50 mg	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab + MTX[b]	116	32	69	15	76
Subjects in response[c]					
Week 64					
ACR 20	73.2% (82/112)	64.5% (20/31)	86.6% (58/67)	53.3% (8/15)	69.3% (52/75)
ACR 50	42.0% (47/112)	35.5% (11/31)	56.7% (38/67)	20.0% (3/15)	48.6% (36/74)
ACR 70	20.5% (23/112)	19.4% (6/31)	35.8% (24/67)	20.0% (3/15)	32.0% (24/75)
Week 76					
ACR 20	71.0% (76/107)	58.6% (17/29)	81.3% (52/64)	50.0% (11/22)	68.6% (48/70)
ACR 50	44.3% (47/106)	27.6% (8/29)	57.8% (37/64)	31.8% (7/22)	51.4% (36/70)
ACR 70	20.6% (22/107)	17.2% (5/29)	35.9% (23/64)	9.1% (2/22)	31.4% (22/70)
Week 88					
ACR 20	71.2% (74/104)	51.7% (15/29)	81.0% (51/63)	54.2% (13/24)	69.6% (48/69)
ACR 50	45.2% (47/104)	34.5% (10/29)	57.1% (36/63)	37.5% (9/24)	49.3% (34/69)
ACR 70	23.1% (24/104)	17.2% (5/29)	38.1% (24/63)	25.0% (6/24)	31.9% (22/69)
Week 100					
ACR 20	70.8% (63/89)	65.5% (19/29)	83.6% (46/55)	66.7% (30/45)	74.2% (49/66)
ACR 50	46.1% (41/89)	41.4% (12/29)	61.8% (34/55)	35.6% (16/45)	50.7% (34/67)
ACR 70	21.3% (19/89)	27.6% (8/29)	40.0% (22/55)	8.9% (4/45)	37.3% (25/67)
Week 104					
ACR 20	67.6% (50/74)	51.7% (15/29)	83.3% (40/48)	62.5% (40/64)	71.6% (48/67)
ACR 50	40.0% (30/75)	37.9% (11/29)	68.8% (33/48)	39.1% (25/64)	50.7% (34/67)
ACR 70	28.0% (21/75)	31.0% (9/29)	50.0% (24/48)	7.8% (5/64)	35.8% (24/67)

[a] This group includes subjects randomized to placebo + MTX who early escaped/crossed over to 50 mg + MTX through the last visit on 50 mg + MTX.
[b] By assigned treatment group as of Week 52.
[c] Subjects are counted in the column through the last visit on that dose.

Patients randomised to golimumab 50 mg + MTX and then switched to golimumab 100 mg + MTX had lower ACR response rates than patients who remained throughout on golimumab 50 mg + MTX, indicating reduced effectiveness in the former group.

The majority of patients (82% to 100%) across all treatment groups who achieved an improved HAQ score at Week 24 maintained the improvement at Week 104.

7.1.2.2.13. Results for other efficacy outcomes

In general, median percent improvement from baseline in CRP and ACR-N index of improvement were maintained over time within each treatment group from Week 52 through Week 104. Overall, the proportion of DAS28 (CRP) responders was maintained in patients receiving golimumab + MTX.

The radiographic findings measured by mean total vdH-S scores at baseline were well balanced between groups. The changes from baseline at Week 52 are shown in the CSR. Changes in the golimumab 50 mg + MTX and golimumab 100 mg + MTX groups were lower but similar to the mean value in the placebo + MTX group. At Week 104, the proportion of patients with no new joint erosions was 67% in the placebo + MTX group, 75.6% in the golimumab + MTX group, and 73.1% in the golimumab 100 mg + MTX group. The proportion of patients with no new JSN was 80.0% in the placebo = MTX group, 81.7% in the golimumab 50 mg + MTX group, and 86.6% in

the golimumab 100 mg + MTX group. The number of patients with no new joint erosions or JSN at Week 104; the changes from baseline in the total vdH-S scores at Week 104 plotted using imputation rules for missing data, and with missing patients excluded, are shown in the CSR. Most patients had no change in vdH-S score and the cumulative probability curves were similar for the placebo + MTX and golimumab + MTX groups (patients randomised to placebo + MTX were switched to golimumab at Week 16). The probability curves were slightly separated at the >90% tail suggesting that radiographic progression was less in the golimumab + MTX groups.

7.1.2.3. Study C0524T12 (GO-LIVE)

7.1.2.3.1. Study design, objectives, locations and dates

This was a multi-centre, randomised, double-blind, placebo-controlled study of golimumab administered IV in patients with active RA despite MTX therapy. It was a 5-arm efficacy and safety study of IV golimumab 2 mg or 4 mg[8] given with or without MTX every 12 weeks, and placebo IV with MTX for a 48 week duration. At Week 16 and Week 24, joint assessments were performed to allow patients into early escape (EE) with dose adjustment in a blinded manner. All patients remained on the same blinded treatment that they received on Weeks 24, 36 and 48 until database lock. No changes to concomitant therapies for RA were allowed. It was conducted at 85 sites in 15 countries in S. America, N. America, Europe and Asia-Pacific countries including Australia and New Zealand.

The primary objective was to assess the efficacy and safety of golimumab IV infusions every 12 weeks with and without MTX, compared with MTX alone, in patients with active RA despite concurrent MTX treatment. The secondary objectives were to evaluate the effects on physical function, QoL, PK, and the PD of IV golimumab. There were no radiological objectives in this study.

7.1.2.3.2. Inclusion and exclusion criteria

Male and female patients aged 18 years or older were eligible. They were required to have active RA and to be on a stable dose of MTX in the range ≥15 mg/week and ≤25 mg/week for at least one month before screening. Key exclusion criteria included active or previous TB; patients with other inflammatory diseases; and patients treated with DMARDs or injected corticosteroids within 4 weeks of screening.[9]

7.1.2.3.3. Study treatments

Patients were randomised to one of five treatment arms as shown below:

[8] IV doses were 2 mg/kg and 4 mg/kg

[9] Sponsor clarification: Sentence should read: *"Key exclusion criteria included active or previous TB; patients with other inflammatory diseases; and patients treated with DMARDs or injected corticosteroids within 4 weeks of the first study agent dose"*

Table 7. Study C0524T12 (GO-LIVE). Treatment arms.

Group I (n = 125):	30-minute IV infusion of 2 mg/kg golimumab at Week 0 and every 12 weeks thereafter through Week 48. In addition, subjects were to receive MTX at the same dose as that before study entry.
Group II (n = 125):	30-minute IV infusions of 2 mg/kg golimumab at Week 0 and every 12 weeks thereafter through Week 48. In addition, subjects were to receive placebo (sham MTX) capsules.
Group III (n = 125):	30-minute IV infusions of 4 mg/kg golimumab at Week 0 and every 12 weeks thereafter through Week 48. In addition, subjects were to receive MTX at the same dose as that before study entry.
Group IV (n = 125):	30-minute IV infusions of 4 mg/kg golimumab at Week 0 and every 12 weeks thereafter through Week 48. In addition, subjects were to receive placebo (sham MTX) capsules.
Group V (n = 125):	30-minute IV infusions of placebo at Week 0 and every 12 weeks thereafter through Week 48. In addition subjects were to receive MTX at the same dose as that before study entry.

7.1.2.3.4. Efficacy variables and outcomes

The primary endpoint was ACR 50 response at Week 14.

Other efficacy variables were:

- ACR 20 responses
- Joint tenderness and swelling measured by DAS28 scores
- Patient's and physician's global assessments of disease activity
- Functional status assessed using HAQ
- QOL assessed by the SF-36 health survey

7.1.2.3.5. Randomisation and blinding methods

Eligible patients were randomised using IVRS. Patients receiving an IV infusion received golimumab or placebo in blinded fashion. Patients received MTX or placebo in matching capsules. Randomisation was stratified by previous use of anti-TNF therapies and investigational site. PK and anti-golimumab antibody data were known only to data management and QA personnel. The database was locked at Week 24 but patients and investigators remained blinded until Week 48.

7.1.2.3.6. Analysis populations

Efficacy analyses were based on the ITT population, namely patients randomly assigned to each treatment group whether or not they received a dose of study treatment. In addition, patients in the randomised treatment groups were evaluated by their EE and /or dose regimen adjustment status.

7.1.2.3.7. Sample size

A total of 625 patients were planned and 643 patients were randomised into the study.

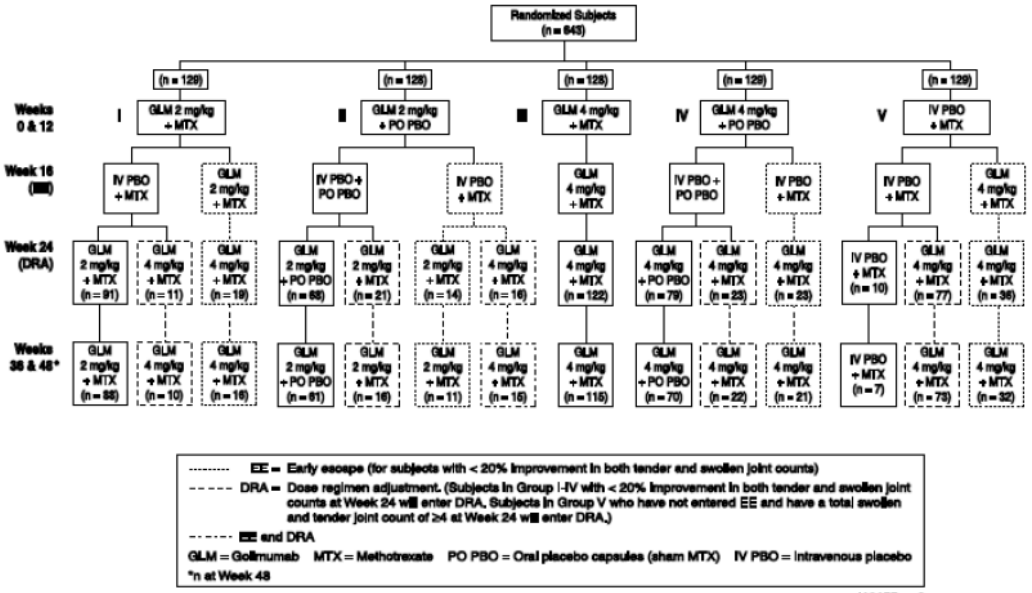
7.1.2.3.8. Statistical methods

Descriptive statistics were used to summarize data. Chi-square or Cochran-Mantel-Haenszel tests were used to compare the proportion of patients achieving specific endpoints between treatment groups. Continuous response parameters were compared by ANOVA. All statistical tests were 2-sided and performed at α=0.05. SAS Version 8.2 was used to conduct the analyses.

7.1.2.3.9. Participant flow

Participant flow is shown below in Figure 8. Of the 643 patients randomised at Week 0, approximately 128 patients were assigned to each treatment group and the majority of patients received their assigned treatment during the first 24 weeks.

Figure 8. Study C0524T12 (GO-LIVE). Subject disposition



A total of 6.1% of patients permanently discontinued IV study treatment through Week 48. More patients discontinued treatment in the combined golimumab + MTX treatment group than in the IV placebo + MTX group (6.2% versus 5.4% respectively). The most common reasons for discontinuing study treatment were AEs, unsatisfactory therapeutic effect, other, and worsening of RA.

7.1.2.3.10. Major protocol violations/deviations

A total of 5.9% of patients did not meet the eligibility criteria. The most frequent deviations were related to medical history. Protocol deviations related to IV study drug administration occurred in 19.3% of the treated patients at Week 24 and they were evenly balanced between treatment groups. The most common deviation was study drug administration outside the specified window (treatment deviations through Week 48 were not tabulated in the CSR).

7.1.2.3.11. Baseline data

The baseline demographics were comparable in each treatment group. Most patients were women (80.4%) and Caucasian (69.5%). The median age was 51.0 years (range 18-77 years) and the median weight was 69.9 kg. Overall, the background medical histories were comparable in each treatment group. Baseline disease characteristics of RA based on ACR criteria are shown in the CSR. Overall, the population had moderate to severe RA. Patients who required early escape at Week 16 had similar baseline characteristics to the main population. The proportions of patients with previous concomitant medications were comparable across treatment groups. The proportion of patients who had used DMARDs, corticosteroids and NSAIDs was 64.4%, 87.1% and 93.5% respectively. The proportion of patients who had previously used MTX for RA for ≥3 years was 48.7%.

7.1.2.3.12. Results for the primary efficacy outcome

The primary endpoint was the ACR 50 response at Week 14. The ACR 50 response of patients randomised to the combined golimumab + MTX groups (2 mg/kg or 4 mg/kg) was not significantly greater than in patients randomised to IV placebo + MTX (21.4% versus 13.2%, respectively, p=0.051).

7.1.2.3.13. Results for other efficacy outcomes

ACR 20 response at Week 14 was achieved by more patients in the combined golimumab + MTX treatment groups (p<0.001) and the combined golimumab + placebo treatment groups (p=0.002) compared with the IV placebo + MTX group. At Week 14, more patients in the combined and individual golimumab treatment groups had a moderate or good response in DAS28 (CRP) compared with the IV placebo + MTX group. At Week 14, more patients had significant improvements in SF-36 and HAQ scores in the individual and combined golimumab + MTX groups compared with the IV placebo + MTX group.

The ACR 20, ACR 50, ACR 70 and ACR 90 responses from Week 24 through Week 48 are shown in Table 8.

Table 8. Study C0524T12. Number of subjects who achieved ACR 20, ARC 50 and ARC 70 responses after Week 24 through Week 48; randomized subjects who did not enter early escape at Week 16 and did not adjust dose regiment at Week 24.

		Golimumab						
	IV Placebo + MTX	Golimumab Only			Golimumab + MTX			All Golimumab
		2 mg/kg	4 mg/kg	Combined	2 mg/kg	4 mg/kg	Combined	
Subjects randomized	16	75	83	158	97	109	206	364
Subjects in response								
Week 36								
n	10	66	76	142	89	102	191	333
ACR 20	7 (70.0%)	29 (43.9%)	41 (53.9%)	70 (49.3%)	58 (65.2%)	73 (71.6%)	131 (68.6%)	201 (60.4%)
ACR 50	6 (60.0%)	16 (24.2%)	15 (19.7%)	31 (21.8%)	28 (31.5%)	43 (42.2%)	71 (37.2%)	102 (30.6%)
ACR 70	5 (50.0%)	7 (10.6%)	4 (5.3%)	11 (7.7%)	11 (12.4%)	17 (16.7%)	28 (14.7%)	39 (11.7%)
ACR 90	0 (0.0%)	1 (1.5%)	1 (1.3%)	2 (1.4%)	1 (1.1%)	2 (2.0%)	3 (1.6%)	5 (1.5%)
Week 48								
n	7	62	72	134	88	98	186	320
ACR 20	5 (71.4%)	31 (50.0%)	37 (51.4%)	68 (50.7%)	59 (67.0%)	69 (70.4%)	128 (68.8%)	196 (61.3%)
ACR 50	5 (71.4%)	15 (24.2%)	16 (22.2%)	31 (23.1%)	32 (36.4%)	47 (48.0%)	79 (42.5%)	110 (34.4%)
ACR 70	2 (28.6%)	8 (12.9%)	8 (11.1%)	16 (11.9%)	10 (11.4%)	17 (17.3%)	27 (14.5%)	43 (13.4%)
ACR 90	0 (0.0%)	3 (4.8%)	2 (2.8%)	5 (3.7%)	4 (4.5%)	4 (4.1%)	8 (4.3%)	13 (4.1%)

RE274 [E_ACR_24_A], 25AUG2008 21:27

The golimumab 4 mg/kg + MTX group had the highest proportion of responders at Week 48. The ACR responses of patients who entered EE at Week 16 had lower response rates at Week 48 than patients who did not enter EE. The proportion of patients achieving ACR 50 response by visit through Week 48 is shown in the CSR. At Week 48, 86.7% of patients who received golimumab 4 mg/kg + MTX had a moderate or good DAS28 (CRP) response. The remaining golimumab groups had lesser responses. There were only 7 patients in the IV placebo + MTX group at Week 48 but all achieved a moderate or good DAS28 response. The majority of patients had a meaningful improvement in HAQ responses from baseline through Week 48. In the combined golimumab + MTX group, the proportion of patients with improvement was 73.1%. For patients who did not enter EE at Week 16 and did not adjust dose at week 24, median changes in SF-36 from baseline through week 48 were highest in the golimumab + MTX groups

7.2. Other efficacy studies

None presented.

7.3. Analyses performed across trials

7.3.1. Golimumab antibodies

In the Phase 3 PsA study, 19 (4.9%) patients developed golimumab antibodies at Week 52 compared with 21 (5.4%) patients at Week 104. In the Phase 3 RA studies golimumab antibodies were detected in 70 (5.3%) patients through Week 52 and 95 (6.6%) patients through Week 104. Patients who received golimumab with MTX had a lower proportion of antibodies (5.3%) than patients who received golimumab without MTX (7.9%). At Week 52, ACR responses were fractionally higher in antibody negative patients but this difference was less apparent at Week 104. The presence of golimumab antibodies did not appear to influence ACR response in RA or PsA although potential effects on radiological scores were not assessed.

7.4. Evaluator's conclusions on clinical efficacy

Progression of structural damage was scored using the vdH-S method which assesses radiographic changes including erosions and JSN in the joints of the hands and feet. In the PsA study C0524T08, a negative mean change from baseline at Week 24 indicated significant inhibition of progression of SD for golimumab 50 mg compared with placebo (p=0.01). Similar changes in the golimumab 100 mg group did not achieve statistical significance. Less progression of SD in golimumab patients was observed with or without MTX when compared with placebo but no additional benefit was observed in patients treated with golimumab 100 mg. From Week 24 to Week 104, there were no control data as all patients were treated with golimumab 50 mg or golimumab 100 mg. In the RA studies C0524T05 and C0524T06, golimumab improved the signs and symptoms at Week 24. In C0524T05 at Week 52, golimumab 50 mg + MTX (p=0.015) and golimumab 100 mg + MTX (p=0.025) significantly reduced the rate of progression of SD measured by vdH-S scores compared with MTX alone. At Week 104, the benefits were maintained. In C0524T06, the rate of progression of structural damage was a secondary endpoint assessed at Week 24. The effects of golimumab could not be assessed because there was minimal SD progression in all treatment groups including the placebo + MTX group. However, there was no evidence that SD progressed in the golimumab groups through Week 104.

The level of evidence supporting inhibition of progression of SD is low because of necessary study design constraints. There were no control groups in the RA and PsA studies from Week 24 to Week 104 and the results were confounded by withdrawals, withdrawals due to lack of efficacy, withdrawals due to AE, early escape in placebo patients, changes in concomitant medications and anti-golimumab antibodies. Nonetheless, the improvement in vdH-S scores observed at Week 24 appeared to be maintained through Week 104 in the majority of RA and PsA patients. Improvements in ACR 20, DAS28 (CRP), HAQ, SF-36 and other efficacy measures at Week 24 were also consistently maintained through Week 104.

Overall, the sustained improvements in symptom and physical scores support the radiological findings. On balance, the combined data support lack of progression of structural damage over a two year period, comparable with the long-term effects of other TNFα inhibitors.

8. Clinical safety

8.1. Studies providing evaluable safety data

The use of TNF inhibitors is associated with AEs of special interest including malignancies and atypical infections. These events occur with a low incidence so pooled data from all RA, PsA and AS pivotal studies are presented. These include:

- The pivotal PsA Phase 3 SC study C0524T08

- The pivotal RA Phase 3 SC studies C0524T05, C0524T06, and C0524T11 including three subsets (MTX-naive patients, MTX-experienced patients, and patients with active RA despite MTX).[10]
- The combined Phase 3 SC studies for all rheumatologic indications: C0524T05 (RA), C0524T06 (RA), C0524T08 (PsA), C0524T09 (AS) and C0524T11(RA)

Three analyses separately evaluating safety data for the PsA and RA indications through Weeks 100/104 are also presented:

- The pivotal PsA Phase 3 SC study C0524T08
- The pooled pivotal RA Phase 3 SC studies C052405, C0524T06 and C0524T11
- The RA Phase 3 IV study C0524T12

8.1.1. Pivotal studies that assessed safety as a primary outcome

NND

8.1.2. Dose-response and non-pivotal efficacy studies

The following dose-response and non-pivotal efficacy studies provided safety data:

- Phase 2b study C0524T01 provided data in patients with uveitis
- Phase 2b study C0524T02 provided data in RA.
- Phase 2b study C0524T03 provided data in patients with severe, persistent asthma.

8.1.3. Other studies evaluable for safety only

NND

8.2. Pivotal studies that assessed safety as a primary outcome

NND

8.3. Patient exposure

In the Phase 3 SC studies of RA, PsA and AS, 1245 patients received golimumab 50 mg and 1377 patients received golimumab 100 mg through week 100/104. The average number of treatment administrations was 16.3 in the golimumab 50 mg group and 18.7 in the golimumab 100 mg group. The median cumulative dose was 950 mg in the golimumab 50 mg group and 2400 mg in the golimumab 100 mg group. Across all the Phase 3 SC rheumatologic studies, the majority of patients were exposed to golimumab for ≥96 weeks (55.9% in RA, 61.9% in PsA and 64.3% in AS). Approximately 25% of the remaining patients were exposed to golimumab for 52 to <96 weeks.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

8.4.1.1.1. Pooled AE data

Data on AEs occurring in ≥5% of treated patients in the combined Phase 3 studies (RA, PsA and AS) through Week 100/104 are provided in the dossier. The proportions of patients who

[10] Sponsor clarification: Sentence should read: *"The pivotal RA Phase 3 SC studies C0524T05, C0524T06, and C0524T11 including three subsets (MTX-naive patients, patients with active RA despite MTX, and anti-TNFα experienced patients"*

reported AEs were 73.4%, 83.0% and 82.6% in the placebo, golimumab 50 mg and golimumab 100 mg groups, respectively (overall exposure was lower in the placebo group compared with the golimumab groups). The system-organ class with the largest proportion of AEs was Infections and Infestations, most commonly upper respiratory infections.

Regarding infections of interest, the incidence (per 100 patient years) of sepsis was 0.28 (95% CI: 0.01, 1.59) in the placebo group, 0.35 (95% CI: 0.13, 0.77) in the golimumab 50 mg group, and 0.51 (95% CI: 0.26, 0.92) in the golimumab 100 mg group. The incidence of pneumonia was 2.56 in the placebo group, 1.89 in the golimumab 50 mg group and 1.68 in the golimumab 100 mg group. The incidence of TB at any site was 0.00 in the placebo group, 0.18 (95% CI: 0.04, 0.52) in the golimumab 50 mg group, and 0.56 (95% CI: 0.29, 0.98) in the golimumab 100 mg group. The incidence of opportunistic infections (including histoplasmosis, Listeria and Legionella infections) was 0.00 (95% CI: 0.00, 0.85) in the placebo group, 0.12 (95% CI: 0.01, 0.43) in the golimumab 50 mg group, and 0.19 (95% CI: 0.05, 0.48) in the golimumab 100 mg group. The 95% CIs for the golimumab groups were fully contained within the placebo group in all categories of infections of interest.

In the combined Phase 2b and Phase 3 rheumatologic studies, there were 46 malignancies in the golimumab groups compared with eight in the placebo group. The incidence of all malignancies (per 100 patient years) was 1.97 in the placebo group compared with 1.06 in the golimumab groups. Allowing for the significant differences in exposure, there were no meaningful differences between groups for all malignancies, lymphoma, non-melanoma skin cancers or other malignancies.

Through Week 100/104, the proportion of patients with injection site reactions was 2.8% in the placebo group, 8.0% in the golimumab 50 mg group and 11.8% in the golimumab 100 mg group. The majority of reactions were of mild intensity. There were 6 moderate reactions in the golimumab 50 mg group, 15 moderate reactions in the golimumab 100 mg group and one severe injection reaction in the golimumab 100 mg group. There were 3 cases of serum sickness and one case of anaphylactic shock. The anaphylaxis occurred 5 weeks after the last dose of study drug during bronchoscopy for suspected pulmonary TB and it was considered unrelated to study treatment by the investigator. Infusion reactions occurred in 4.2% of golimumab patients compared with 5.4% of patients who received IV placebo + MTX.

8.4.1.1.2. AE profile in PsA

The key safety data reported in the pivotal PsA study C0524T08 are provided in the submission. Exposure to placebo was limited compared with patients who received golimumab so the comparative safety data are of limited value. AEs were reported in 61.1% of placebo patients compared with 78.2% and 70.9% in the golimumab 50 mg and 100 mg groups respectively. The incidence of serious infections was higher in the placebo group compared with patients who received placebo. Eight malignancies were reported in the golimumab groups compared with none in the placebo patients.

8.4.1.1.3. AE profile in RA

The AE profiles were similar in the three pivotal RA studies C0524T05, C0524T06 and C0524T11. Key safety data are reported in the combined RA studies. Exposure to placebo was limited compared with patients who received golimumab so the comparative safety data are of limited value. AEs were reported in 75.9% of placebo patients compared with 82.1% and 83.0% in the golimumab 50 mg and 100 mg groups respectively. The incidence of serious infections was less in the placebo group (2.7%) compared with patients who received golimumab 50 mg (4.7%) and 100 mg (7.0%). Six malignancies were reported in the placebo group compared with 14 patients in the golimumab 50 mg group and 16 patients in the golimumab 100 mg group. However, the incidence of serious infections per 100 patient years was similar in all groups.

Note: There were numerical but no clinically meaningful differences between the AE profiles in patients with PsA and RA.

8.4.1.2. Other studies

In the Phase 3 RA IV study C0524T12, from Week 0 to Week 48 the average duration of follow-up was 23.1 weeks in the placebo group and 42.3 weeks in the combined golimumab groups. AEs were recorded in 72.1% of the IV placebo + MTX patients 81.6% of all patients who received golimumab. There was no relationship between dose and AE rates. The most common AE classification was infections and infestations which occurred in 41.1% of placebo patients and 47.9% of the combined golimumab group. The most common infections were upper respiratory infections which occurred in 9.3% of the placebo group and 11.7% of the combined golimumab group. Malignancies occurred in two patients (1.6%) in the IV placebo + MTX group and 8 patients (1.3%) in the combined golimumab group.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

No new ADRs were identified through Week 100/104.

8.4.2.2. Other studies

No new ADRs were identified.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

8.4.3.1.1. Pooled data

There were 16 deaths in the combined (RA, PsA and AS) studies of SC golimumab, and a further 5 deaths in the Phase 3 IV RA study. When all the rheumatologic Phase 2b and Phase 3 studies were combined, the incidence of deaths per 100 patient years was 0.25 (95% CI: 0.01, 1.37) in the placebo group (803 subjects) and 0.46 (95% CI: 0.28, 0.71) in the golimumab group (2985 subjects). Most deaths were due to cardiac disorders and malignancies.

In the combined Phase 2b and Phase 3 rheumatologic studies, SAEs other than death were reported in 8.0%, 12.0% and 16.4% of the placebo, golimumab 50 mg and golimumab 100 mg groups respectively. As noted previously, exposure was more than two fold higher in the golimumab groups compared with the placebo group. Among patients treated with golimumab, infections occurred most frequently in the Infections and Infestations system-organ class (2.7% in the placebo group, 3.1% in the golimumab 50 mg group and 5.7% in the golimumab 100 mg group).

8.4.3.1.2. Pivotal PsA study

Data on deaths and SAEs in the pivotal Phase 3 PsA study C0524T08 are provided. There were two deaths (one lung carcinoma and one accidental death), both in patients who received golimumab 50 mg. The incidence of SAEs was similar in patients who received placebo (7.1%), golimumab 50 mg (6.5%) and golimumab 100 mg (7.9%).

8.4.3.1.3. Phase 3 RA studies

Deaths and SAEs in the three pivotal Phase 3 RA studies (C0524T05, C0524T06 and C0524T11) are provided. There was one death in the placebo group compared with four and eight deaths in the golimumab 50 mg and 100 mg groups respectively. SAEs were reported in 9.6%, 14.9% and 18.7% in the placebo, golimumab 50 mg and golimumab 100 mg groups respectively. Most SAEs were categorised as Infections or Infestations.

Comment: The incidence of SAEs was higher in RA patients compared with PsA in all groups. However, there were no clinically meaningful qualitative differences in the AE profiles in patients with PsA and RA.

8.4.3.2. Other studies

Three deaths (each due to myocardial infarction) were recorded in the IV RA study C0524T12. The patients had each received golimumab but the investigators considered the events to be unrelated to drug. SAEs were reported more commonly in the golimumab groups (10.1%) than in the IV placebo + MTX group (5.4%). The SAE profile was similar in golimumab and IV placebo + MTX groups with the exception of infections (3.7% and 1.6% respectively).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

Discontinuations due to adverse events are reported in the individual study efficacy evaluations above.

8.4.4.2. Other studies

Discontinuations due to adverse events are reported in the individual study efficacy evaluations above.

8.4.5. Laboratory tests

8.4.5.1. Liver function

8.4.5.1.1. Pivotal studies

In the combined rheumatologic SC Phase 3 studies through Week 100/104, the most frequently abnormal chemistry value in golimumab treated patients was elevated total bilirubin [2 patients (0.3%) in the placebo group, 6 patients (0.5%) in the golimumab group, and 13 patients (1.0%) in the golimumab 100 mg group]. Most patients who had a normal ALT at baseline remained below ULN through Week 100/104. A total of 23.4%, 39.9% and 36.6% of patients had at least one ALT elevation during the course of the study in the placebo, golimumab 50 mg and golimumab 100 mg groups respectively. Most ALT elevations were mild (<x2 ULN). One patient (0.2%) in the placebo group, 2 patients (0.2%) in the golimumab 50 mg group and 7 patients (0.6%) in the golimumab 100 mg group had severe ALT elevations ≥x8 ULN. Post-baseline ALT elevations in the range ≥x5 ULN to <x8 ULN occurred in 3 patients (0.5%) in the placebo group, 14 patients (1.2%) in the golimumab 50 mg group, and 8 patients (0.7%) in the golimumab 100 mg group. Most patients who had an elevated ALT at baseline had at least one abnormal post-baseline measurement but no patient had a post-baseline ALT elevation ≥x8 ULN. The incidence of ALT elevations ≥x5 ULN per 100 patient years was 2.06 (95% CI: 0.83, 4.25) in the placebo group, 1.84 (95% CI: 1.24, 2.63) in the golimumab 50 mg group, and 1.16 (95% CI: 0.74, 1.73) in the golimumab 100 mg group.

8.4.5.1.2. Other studies

In study C0524T12, the incidence of LFT abnormalities was similar in the golimumab treatment groups (45.1%) and the IV placebo + MTX group (41.7%). Two patients in the golimumab 2mg/kg + MTX group (1.4%) had ALT elevations >x8 ULN but marked LFT abnormalities were otherwise unusual.

8.4.5.2. Kidney function

8.4.5.2.1. Pivotal studies

There were no cases of treatment emergent significant impairment of renal function.

8.4.5.2.2. Other studies

In study C0524T12, there were no cases of treatment emergent significant impairment of renal function.

8.4.5.3. Other clinical chemistry

8.4.5.3.1. Pivotal studies

The proportion of patients with markedly abnormal clinical chemistry values was low and no patient had >1 markedly abnormal chemistry value. The most commonly occurring abnormal chemistry value was creatinine kinase which increased 3.5 x ULN in 3 (15.8%) patients in the golimumab 100 mg group. The proportions of patients with markedly abnormal laboratory values were similar in the placebo and golimumab treatment groups.

8.4.5.3.2. Other studies

In study C0524T12, there were no cases of treatment emergent significant abnormalities in clinical chemistry.

8.4.6. Haematology

8.4.6.1. Pivotal studies

In the combined rheumatologic Phase 3 SC studies through Week 100/104, decreased haematocrit occurred in 3 patients (0.5%) in the placebo group and 21patients (0.9%) in the combined golimumab groups. Decreased neutrophil counts occurred in 2 patients (0.3%) in the placebo group and 28 patients (1.3%) in the combined golimumab group. Elevated eosinophils occurred in 1 patient (0.2%) in the placebo group and 22 patients (1.0%) in the combined golimumab group.

8.4.6.2. Other studies

In study C0524T12, there were no cases of treatment emergent significant haematological abnormalities. There were minor increases in serum haemoglobin from baseline in the golimumab groups compared with placebo although the differences were not statistically significant.

8.4.7. Other laboratory tests

NND

8.4.8. Electrocardiograph

8.4.8.1. Pivotal studies

ECG changes were reported as AEs if they were considered clinically significant. There is no systematic review of ECG data in the safety data submitted.

8.4.8.2. Other studies

In study C0524T12, ECG changes were reported as AEs if they were considered clinically significant. There is no systematic review of ECG data in the safety data submitted. At Week 48, cardiovascular events were reported in 1/129 (0.8%) patient in the IV placebo + MTX group and 2/129 (1.6%) patients in the golimumab groups.

8.4.9. Vital signs

8.4.9.1. Pivotal studies

Changes in vital signs were reported as AEs if they were considered clinically significant. There is no systematic review of vital signs in the safety data submitted.

8.4.9.2. Other studies

In study C0524T12, changes in vital signs were reported as AEs if they were considered clinically significant. There is no systematic review of vital signs in the safety data submitted.

8.5. Post-marketing experience

Post-marketing data are not included in this submission as golimumab has only been recently marketed. The data will be summarised in separate PSURs

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

There was no evidence of liver toxicity following long-term treatment with golimumab in the clinical trial data submitted (as discussed above).

8.6.2. Haematological toxicity

There was no evidence of haematological toxicity following long-term treatment with golimumab in the clinical trial data submitted..

8.6.3. Serious skin reactions

The proportions of patients with skin AEs were similar in placebo and golimumab patients. Skin and subcutaneous disorders occurred in 15.8% of placebo patients compared with 17.6% of patients treated with golimumab 50 mg and 22.3% of patients treated with golimumab 100 mg. Rash occurred in 4.0% of placebo patients, 4.2% of patients treated with golimumab 50 mg, and 5.5% of patients treated with golimumab 100 mg.

8.6.4. Cardiovascular safety

No cardiac safety signals were observed during long-term treatment with golimumab in the clinical trial data submitted.

8.6.5. Unwanted immunological events

A small proportion of patients had injection site reactions or infusion reactions in placebo and golimumab patients (discussed in the relevant sections above).

8.7. Other safety issues

8.7.1. Safety in special populations

The impact on safety of golimumab was assessed in subpopulations based on gender, race, age and body weight. There was no clinically meaningful evidence of a gender effect. In the golimumab 50 mg group in the combined rheumatologic studies, 81.7% of males and 83.7% of females had AEs, 9.7% of males and 13.3% of females had SAEs, and 4.4% of males and 7.3% of females had AEs leading to discontinuation. Similar minor differences were apparent in the golimumab 100 mg group. Most patients were Caucasian while the rest were mainly Asian. There were no obvious differences in AE profile between these groups. The majority of patients were <65 years old and few were >75 years old. There was a trend towards higher numbers of SAEs and serious infections in patients who were ≥75 years of age. No relationship between safety and body weight was observed.

8.7.2. Safety related to drug-drug interactions and other interactions

NND

8.8. Evaluator's overall conclusions on clinical safety

In the long-term extension studies in RA and PsA, 825/1475 patients were treated with golimumab 50 mg or 100 mg for 2 years although no patients in any study received placebo for more than 52 weeks. AEs were reported slightly more frequently in the golimumab groups compared with placebo, mainly due to infections. The incidence of deaths and SAEs was low but

approximately two-fold higher in the golimumab groups compared with placebo. Deaths were most commonly due to cardiac causes or malignancies while SAE due to infections were more common in the golimumab group. A total of 46 malignancies occurred in the golimumab group compared with eight in the placebo group. However, the incidence per 100 patient years was numerically lower in the golimumab group than in the placebo group. Allowing for the significant differences in exposure, there were no meaningful differences in the incidence of specific tumour types including tumours such as lymphoma which are associated with RA. There were no cases of TB or opportunistic infections in the placebo group although exposure was limited. In the combined golimumab group there were meaningful but low numbers of TB and opportunistic infections as expected for golimumab and other TNFα inhibitors. Interpretation of safety is confounded by the lack of adequate control data. However, no new or unexpected safety signals emerged during the two year extension studies in RA or PsA.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of golimumab in the proposed usage are:

- Long-term improvement in signs and symptoms of RA and PsA (including rash)
- Long-term improvement in physical function
- Long-term improvement in QoL
- Inhibition of progression of structural damage over a 2 year period

9.2. First round assessment of risks

The risks of golimumab in the proposed usage are:

- New or re-activation of latent TB
- Opportunistic infections such as Legionella, histoplasmosis and Listeria
- Possible long-term risk of malignancy
- Allergic and other infusion-like reactions

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of golimumab, given the proposed usage, is favourable. A majority of patients maintained improvements of symptoms, physical function and structural damage in the long-term extension studies of up to 2 years in RA and PsA. The risks are those shared by other marketed anti-TNFα agents and no product specific signals have been detected. The potential risks of golimumab therapy are adequately addressed in PRECAUTIONS in the approved PI.

10. First round recommendation regarding authorisation

Approval of the new indication is recommended.

11. Clinical questions

11.1. Additional expert input

The sponsor is requested to provide to the TGA a copy of the Complete Response Letter issued by the FDA with regard to the inhibition of structural damage as well as a response from the sponsor to each of the issues raised in that Complete Response Letter.

11.2. Pharmacokinetics

If dose linearity was available in previous studies, these data should be provided by the sponsor.

11.3. Pharmacodynamics

No questions.

11.4. Efficacy

No questions.

11.5. Safety

No questions.

11.6. PI and CMI

The sponsor should provide a justification for not giving greater weight to the week 104 data in the proposed PI. An amended PI from the sponsor (for the 50mg groups alone) should also be provided, including a summary of what radiographic changes (joint narrowing, etc) were assessed with the results at 52 and 104 weeks, compared with baseline and a summary table of vdH-S scores at 52 and 104 weeks compared with baseline.[11]

12. Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to the TGA's S31 request are summarised below:

1. *Please provide to the TGA a copy of the Complete Response letter issued by the FDA with regard to the inhibition of structural damage as well as your response as the sponsor to each of the issues raised in that Complete Response Letter.*

The sponsor provided a copy of the CRL and their response to the FDA. The FDA considers that the data do not provide substantial evidence to support a claim for radiographic response in patients with rheumatoid arthritis for Simponi. Their main concerns relate to changes in vdH-S scores which were small and inconsistent with no long-term blinded, control data study. For example, in study C0524T05 treatment benefits in favour of golimumab 50mg + MTX were statistically significant in the PP set but not in the ITT set. In addition, treatment effects were lower in the golimumab 100mg + MTX group than in the golimumab 50mg + MTX group which can be considered biologically implausible. They also noted that changes in vdH-S scores from baseline to Week 104 were minimal in all treatment groups in C0524T06. The same arguments are presented for rejecting the PsA study data. For both RA and PsA indications, the FDA also

[11] Note that the section discussing PI and CMI is not included in this extract from the CER.

faults the lack of statistical adjustment for multiplicity (the likelihood of chance positive findings when measuring multiple efficacy end-points).

The sponsor has responded that in study C0524T05, the marginal lack of significance in the ITT set need not invalidate the significant benefit observed in the PP set. They postulate that the relative lack of benefit for structural damage in the golimumab 100mg group is likely to be an artefact because overall the ACR20 and HAQ efficacy data showed significant benefit compared with placebo. They argue that structural changes are inevitably small when assessments are measured over only a 24 or 52 week period. They also argue that repeated radiological evaluations of small changes are inevitably subject to intra- and inter-observer error despite all best efforts to minimise them. No cogent arguments are provided by the sponsor to refute the possibility of multiplicity.

The sponsor argues that it is unethical and impractical to conduct long-term placebo controlled studies in patients with active disease. They also argue that inhibition of structural damage has been approved for other TNF inhibitors without long-term controlled data. They point out that the EMA and Canadian authorities have accepted these arguments and approved the inhibition of structural damage indication for Simponi.

The arguments presented by the FDA are scientifically sound and reasonable. However, overall the evidence suggests that in patients with RA and PsA who are treated with golimumab 50mg + MTX, there is an early improvement in signs, symptoms, functional activity and inhibition of structural damage. Long-term controlled data are not available but 70 – 80% of patients treated with golimumab 50mg + MTX maintain superior early treatment benefits when compared with MTX alone, and continue to have worthwhile disease control at 104 weeks.

Despite the numerous confounding factors considered in the first round evaluation, the balance of evidence supports the proposed indication of inhibition of structural damage.

2. *If data on dose linearity was available in previous studies/submissions, you are requested to supply a summary of the relevant data. If the latter consists of data which has not been previously evaluated by the TGA, please identify that data.*

The sponsor states that the dose proportionality of golimumab was assessed in the original Week 24 submission (PM-2008-01811-3). In summary, in study C0466T02 dose proportionality for both C_{max} and AUC_{inf} was established following SC administration of 0.3, 0.6 and 3.0 mg/kg doses in healthy volunteers. Dose proportionality of 50 and 100mg doses was also demonstrated in Caucasian and Japanese healthy volunteers in study C0524T23.

13. Second round benefit-risk assessment

No change from first round assessment.

13.1. Second round assessment of risks

No change from first round assessment.

13.2. Second round assessment of benefit-risk balance

The risk-benefit balance of golimumab in the proposed usage is favourable.

13.3. Second round recommendation regarding authorisation

Approval of the new indication is recommended.

14. References

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2. Breedveld FC, *et al*. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone in patients with early, aggressive, rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* (2006) 54(1):26-37
3. Klareskog L, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomized control trial. *Lancet* (2004) 363:675-681
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6. Mease PJ, *et al.* Etanercept treatment of psoriatic arthritis, safety, efficacy, and effect on disease progression. *Arthritis Rheum* (2004) 50(7):2264-2272
7. Mease PJ, *et al*. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis, results of double-blind, randomized, placebo-controlled trial. *Athritis Rheum* (2005) 52(10):3279-3289

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