Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Golimumab (rmc)

Proprietary Product Name: Simponi and Simponi Smartject Injector

Sponsor: Janssen-Cilag Pty Ltd

August 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 AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission 4
Submission details 4
Product background 5
Regulatory status 6
Product Information 6
II. Quality findings 6
III. Nonclinical findings 6
IV. Clinical findings 6
Introduction 6
Clinical rationale 6
Contents of the clinical dossier 7
Pharmacokinetics 8
Pharmacodynamics 9
Efficacy 9
Safety 11
List of questions and Second round evaluation of clinical data submitted in response to questions 13
Second round recommendation regarding authorisation 14
V. Pharmacovigilance findings 14
VI. Overall conclusion and risk/benefit assessment 14
Quality 14
Nonclinical 14
Clinical 14
Risk Management Plan 33
Risk-benefit analysis 33
Outcome 41
Attachment 1. Product Information 43
Attachment 2. Extract from the Clinical Evaluation Report 43

I. Introduction to product submission

Submission details

Type of Submission:	Extension of indications and updates to Product Information
Decision:	Approved
Date of Decision:	9 July 2013
Active ingredient:	Golimumab (rmc[1])
Product Names:	Simponi, Simponi Smartject Injector
Sponsor's Name and Address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
Dose form:	Solution for injection
Strength:	50 mg/0.5 mL
Containers:	Prefilled injector pen and prefilled syringe
Pack sizes:	1 and 3
Approved extension to therapeutic use (amendment bolded):	*Rheumatoid arthritis (RA)* Simponi, in combination with methotrexate, is indicated for: The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate. **Simponi has also been shown to inhibit the progression of joint damage as measured by X-ray.** ***Psoriatic arthritis (PsA)*** Simponi, alone or in combination with methotrexate, is indicated for: The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. **Simponi has also been shown to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease, and improve physical function.**
Route of administration:	Subcutaneous injection
Dosage (abbreviated):	50 mg once a month
ARTG Numbers:	153181 and 153767

[1] RMC denotes production using recombinant mouse cells

Product background

Golimumab is a human immunoglobulin (Ig) G1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant deoxyribonucleic acid (DNA) technology. It forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human tumour necrosis factor (TNF), which prevents the binding of TNF to its receptors. Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis (RA), as well as spondyloarthropathies such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS), and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

Golimumab is currently registered as a solution for subcutaneous (SC) injection in 50 mg/0.5 mL Simponi prefilled syringe and Simponi Smartject prefilled injector pen, for the following indications:

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

This AusPAR describes the application by Janssen-Cilag Pty Ltd (the sponsor) to amend the wording of the indications for RA and PsA as follows (proposed amendments in bolded text:

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

The sponsor also proposed to add new information for RA and PsA to the *Clinical Trials* section of the Product Information (PI).[2]

No changes are proposed regarding the indication for ankylosing spondylitis.

[2] With the exception of changes to the *Indications*, details of revisions to the PI are beyond the scope of the AusPAR

Regulatory status

Simponi golimumab (rmc) 50 mg solution for injection pre-filled syringe and Simponi Smartject injector golimumab (rmc) 50 mg solution for injection pre-filled pen received initial registration on the Australian Register of Therapeutic Goods on 13 November 2009.

At the time the current application was considered by the TGA, an application to include wording relating to structural damage in the RA and PsA indications was approved in the EU (2011), Canada (2011) and Switzerland (2012).

In the US, the FDA had issued a Complete Response Letter (in July 2011 for the RA indication and September 2011 for the PsA indication) requesting the sponsor provide *"additional information in order to move forward with evaluation of the sBLA [supplemental biologic license application] for Structural Damage in RA".* At that time, the sponsor was still in discussions with the FDA.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The sponsor seeks to extend the indications of Simponi by inclusion of *inhibition of structural damage* under both RA and PsA indications. 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*.

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 (MTX), local or systemic steroids, non steroidal anti-inflammatory drugs (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 RA, PsA

and 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 quality of life 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. 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.

Contents of the clinical dossier

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, C0524T11).
- A corrective update on the GO-AFTER study (previously evaluated by the TGA).
- One pivotal Phase 3 study in patients with PsA (C0524T08).
- Additional safety data are included from studies C0524T09 (AS) and C0524T12 (RA, 48 Weeks).
- Literature references

Module 1

- Application letter, application form, draft Australian PI and Consumer Medicine Information (CMI), and overseas regulatory status.

Module 2

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

Guidance

A pre-submission planning form for the extended indications was lodged with the TGA in March 2012. Guidance included several TGA-adopted guidelines of the European Medicines Agency (EMA) Committee for Medicinal Products for Human use (EMA/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.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

Table 1. Submitted pharmacokinetic (PK) 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 golimumab SC 100 mg every 4 weeks and IV 2 mg/kg on Days 1 and 85 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 PK studies had deficiencies that excluded their results from consideration.

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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 % coefficient of variation (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).

Pharmacodynamics

Table 2. Submitted pharmacodynamic (PD) studies

PD Topic	Subtopic	Study ID	Primary Aim of Study
Primary Pharmacology	PK comparison of multiple doses of SC and IV golimumab Effect on serum biomarkers	C0524T14 C0524T14	PK/PD of golimumab SC 100 mg every 4 weeks and 2 mg/kg IV on Days 1 and 85 in patients with RA
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 PD studies had deficiencies that excluded their results from consideration.

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 once every 12 weeks (q12 week) 2 mg/kg intravenous (IV) dosing. The study did not test the 50 mg SC once monthly regimen used in the Phase III studies.

Efficacy

Studies providing evaluable efficacy data

The following pivotal efficacy studies were provided:

Active psoriatic arthritis

- **Study C0524T08 (GO-REVEAL)**

This is an on-going multicentre, randomized, double-blind, placebo-controlled Phase III trial of golimumab in adult patients with active PsA. The study was designed to compare the efficacy, safety and clinical pharmacology of golimumab 50 mg or 100 mg given SC every 4 weeks. Patients were randomly assigned and stratified according to concomitant MTX use.

The primary objectives of the study were:

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

Rheumatoid arthritis

- **Study C0524T05 (GO-BEFORE)**

This is an ongoing Phase III, multi-centre, randomised, double-blind, placebo-controlled, 4 arm trial of SC golimumab in MTX-naïve patients with active RA. 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 in combination with MTX. In addition, a golimumab 100 mg without MTX arm was also evaluated.

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.

- **Study C0524T06 (GO-FORWARD)**

This is an on-going Phase III, 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 RA despite MTX therapy. In addition, a golimumab 100 mg without MTX arm was also evaluated.

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.

- **Study C0524T12 (GO-LIVE)**

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/kg or 4 mg/kg given with or without MTX every 12 weeks, and placebo IV with MTX for a 48 week duration.

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.

Details of the above studies are found in AusPAR Attachment 2, Extract from the Clinical Evaluation Report (CER).

Evaluator's overall conclusion on efficacy

Progression of structural damage was scored using the van der Heijde-Sharp (vdH-S) (score) method which assesses radiographic changes including erosions and joint space narrowing (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 structural damage 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 structural damage 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 structural damage measured by vdH-S scores compared with MTX alone. At Week 104, the benefits were maintained. In Study 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 structural damage progression in all treatment groups including the placebo + MTX group. However, there was no evidence that structural damage progressed in the golimumab groups through Week 104.

The level of evidence supporting inhibition of progression of structural damage 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 adverse events (AEs), 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 American College of Rheumatology (ACR[4]) 20, Disease Activity Score including evaluation of 28 joints (DAS28) and C-reactive protein (CRP), Health Assessment Questionnaire (HAQ), 36-item short form health survey (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.

Safety

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 in the submission. These include:

- The pivotal PsA Phase III SC Study C0524T08
- The pivotal RA Phase III SC Studies C0524T05, C0524T06, and C0524T11 including three subsets (MTX-naïve patients, MTX-experienced patients, and patients with active RA despite MTX).[5]

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

[5] 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"*

- The combined Phase III SC studies for all rheumatologic indications: Studies 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 III SC Study C0524T08
- The pooled pivotal RA Phase III SC Studies C052405, C0524T06 and C0524T11
- The RA Phase 3 IV study C0524T12

Dose-response and non-pivotal efficacy studies

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

- Phase IIb Study C0524T01 provided data in patients with uveitis
- Phase IIb Study C0524T02 provided data in RA
- Phase IIb Study C0524T03 provided data in patients with severe, persistent asthma

Patient exposure

In the Phase III 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 III 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.

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. Adverse events were reported slightly more frequently in the golimumab groups compared with placebo, mainly due to infections. The incidence of deaths and serious AEs (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 SAEs 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 tuberculosis (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.

List of questions and Second round evaluation of clinical data submitted in response to questions

The clinical evaluator raised two specific questions following the first round assessment phase. The clinical evaluator's assessment of the sponsor responses to these appears 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 has provided a copy of the Complete Response Letter (CRL) and the 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 or PsA 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 RA Study C0524T05 treatment benefits in favour of golimumab 50 mg + MTX were statistically significant in the per protocol (PP) set but not in the intention to treat (ITT) set. In addition, in the PsA Study C0524T08, treatment effects were lower in the golimumab 100 mg group than in the golimumab 50 mg 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 RA Study C0524T06. For both RA and PsA indications, the FDA also faults the lack of statistical adjustment for multiplicity (the likelihood of chance positive findings when measuring multiple efficacy end-points).

The sponsor 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 100 mg group is likely to be an artefact because overall the ACR 20 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 European Medicines Agency (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 50 mg + 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 50 mg + 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 stated that the dose proportionality of golimumab was assessed in the original Week 24 submission for the registration of golimumab. In summary, in Study

C0466T02 dose proportionality for both the maximum plasma concentration (C_{max}) and area under the concentration-time curve to infinity (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 100 mg doses was also demonstrated in Caucasian and Japanese healthy volunteers in Study C0524T23.

Second round benefit-risk assessment

No change from first round assessment.

Second round assessment of risks

No change from first round assessment.

Second round assessment of benefit-risk balance

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

Second round recommendation regarding authorisation

Approval of the new indication is recommended.[6]

V. Pharmacovigilance findings

A Risk Management Plan (RMP) was not required to be submitted for this application.

VI. Overall conclusion and risk/benefit assessment

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

In the Overview, the Delegate raised several matters that the sponsor was requested to address. These matters are presented below in bolded text.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Golimumab is a human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology. It forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF, which prevents the binding of TNF to its receptors.

According to the clinical evaluation report (CER), the clinical data consisted of:

[6] Note that the evaluator's discussions and recommendations regarding revisions to the PI and CMI are beyond the scope of the AusPAR.

- 1 clinical pharmacology study to compare the PK/PD of SC versus IV golimumab in RA patients (Study C0524T14) and 1 study to assess the absolute bioavailability of SC golimumab in healthy subjects (Study C0524T15)
- 3 pivotal Phase III studies in patients with RA (Studies C0524T05 or GO-BEFORE, C0524T06 or GO-FORWARD and C0524T11 or GO-AFTER)
- A corrective up-date to Study C0524T11 or GO-AFTER in subjects with active RA (previously evaluated by the TGA)
- 1 pivotal Phase III study in patients with PsA (C0524T08)
- Additional safety data included from Studies C0524T09 (AS) and C0524T12 (RA, 48 weeks)
- Supportive literature references in Module 5.4

The sponsor's application letter provides an overall view of the clinical data thus:

- Data which directly supports the application to change the indications and which supports the other proposed changes to the PI:
  - RA – Study C0524T05 or GO-BEFORE evaluated 637 patients with active RA who were MTX-naive and had not previously been treated with an anti-TNF agent. From this study 52-week [and 104 week] radiographic data is being submitted as well as co-primary endpoint efficacy data for signs and symptoms and secondary measures of physical function and health-related QoL.
  - RA – Study C0524T06 [GO-FORWARD] evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX. In this application, the sponsor is submitting follow-up 52-week [and 104 week] radiographic data
- Other studies included in the dossier, that is, studies which were included in the submission as they were referred to in the dossier and were part of the global dossier submitted overseas but which do not support any of the proposed changes to the PI.

Relevant EU Guidelines (beside general guidelines) are as follows (please note that there is a specific guideline for each of RA, PsA and AS):

- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a (pdf,27kb)
  Clinical Investigation of Medicinal Products for Long-Term Use
  Effective: 12 February 2002
- See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)
- pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (pdf,25kb)
  The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions
  Effective: 12 February 2002
  Adopted by the TGA with conditions.

  See also: pp.127 - 132 of Rules 1998 3C - 3CC6a
- CPMP/EWP/556/95 Rev 1 (pdf,176kb)
  Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. December 2003.
- EMEA/CHMP/EWP/438/04 (pdf,125kb)
  Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis December 2006.

- CPMP/EWP/4891/03 (pdf,78kb)
  Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Aprill 2009.

Pharmacokinetics

The purpose of Study C0524T15 was to assess the absolute bioavailability of a single SC administration of golimumab 100 mg in healthy subjects. The absolute bioavailability was determined to be 51%. As noted by the clinical evaluator, the study formed part of the global golimumab submission and was included in this submission for completeness. There are no changes to the PI proposed in this submission arising from the results of this study. Bioavailability of the 100 mg SC dose was thought to be comparable to that of the marketed 50 mg dose although there was no direct evidence of that comparability provided in this submission. As a result the clinical evaluator did ask a question of the sponsor on this issue (see *Second round clinical evaluation,* below). Briefly, evidence of dose proportionality had been provided in the original submission for registration.

Pharmacodynamics

Study C0524T14 was an open-label, randomised, multiple dose study to investigate the PK and PD of both SC and IV administration of golimumab in patients with RA. There were clinically meaningful improvements in clinical indices of disease activity (DAS28) but no meaningful statistical correlations between those clinical indices and serum biomarkers. This is perhaps not altogether surprising. **However, the sponsor was requested to provide some comment on this issue in the response to this Overview.**

Efficacy

Active psoriatic arthritis

Study C0524T08 (GO-REVEAL)

This is an on-going multicentre, randomised, double-blind, placebo-controlled Phase III trial of golimumab in adult patients with active PsA. The study was designed to compare the efficacy, safety and clinical pharmacology of golimumab 50 mg or 100 mg given SC every 4 weeks. 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 (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 randomised 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.

Radiographic assessment of structural damage was based on X-rays of hands and feet using the 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 primary objectives of the study were:

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

There were a number of secondary objectives.

Male and female patients aged 18 years or older with active PsA despite current or previous DMARD or NSAID therapy were eligible to enrol. Exclusion criteria included prior exposure to anti-TNFα therapy. **The sponsor was asked to clarify whether the patient population consisted of only those with polyarticular symmetrical subtypes of the disease.**

The co-primary efficacy outcomes were:

- Change from baseline in total modified vdH-S scores at Week 24.
- The proportion of patients with ACR 20 response at Week 14

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.[7]

A total of 405 patients were randomised to treatment. 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.

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.

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.

[7] 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.*

Table 3. Reporting of radiographic endpoints in Study C0524T08 (PsA). 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
Randomized subjects (Reading Session 2)[c]	89	120	130	250
Baseline[d]				
n	89	120	130	250
Mean ± SD	16.34 ± 26.680	22.99 ± 35.286	20.44 ± 35.726	21.66 ± 35.467
Median	9.00	10.00	5.50	7.00
IQ range	(2.50, 18.50)	(2.00, 26.50)	(1.50, 21.50)	(1.50, 22.50)
Range	(0.0, 183.0)	(0.0, 190.0)	(0.0, 218.9)	(0.0, 218.9)
Week 52[d]				
n	89	119	130	249
Mean ± SD	16.59 ± 26.576	23.45 ± 35.820	20.08 ± 35.189	21.69 ± 35.461
Median	9.00	9.16	5.50	7.00
IQ range	(2.50, 19.12)	(2.00, 28.50)	(1.50, 22.00)	(1.50, 23.50)
Range	(0.0, 180.5)	(0.0, 188.5)	(0.0, 215.8)	(0.0, 215.8)
Week 104[d]				
n	89	120	130	250
Mean ± SD	16.56 ± 26.555	23.17 ± 35.773	20.11 ± 35.240	21.58 ± 35.459
Median	9.00	9.08	5.50	7.00
IQ range	(2.06, 20.00)	(2.00, 27.75)	(1.50, 21.50)	(1.50, 23.00)
Range	(0.0, 180.5)	(0.0, 188.5)	(0.0, 216.2)	(0.0, 216.2)

		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 (intention to treat), 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 the CER. 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%).

Results for other efficacy outcomes were encouragingly supportive. The proportion of patients who achieved an ACR response at Week 14 was maintained up to Week 104. Likewise the proportion of patients with a DAS28 (CRP) response was maintained after Week 52 through Week 104 in all treatment groups. The proportion of patients with Psoriasis Area and Severity Index (PASI) response was maintained after Week 52 through Week 104 in each treatment group.

Delegate's comments on radiographic findings of Study C0524T08 (study on PsA)

The relevant EU guideline to do with PsA (CHMP/EWP/438/04) endorses the use of the vdH-S modified scoring method. The latter is an assessment of structural damage in peripheral joints in PsA but it does not assess any spinal or sacro-iliac joint abnormalities in PsA. Thus any reporting of the findings of the study in the PI and indeed the wording of the indications should reflect that limitation. A useful guide in this respect is the wording adopted in the EU Summary of Product Characteristics (SmPC) for golimumab, where the wording for the PsA now includes *"Simponi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease"*.

With regard to the actual ability to make an additional claim to prevent structural damage, the guideline states that radiographs should be taken on fixed and predefined time points and be assessed by at least two assessors, appropriately blinded. These requirements were satisfied. The guideline does not specify the degree of separation of the time points.

The guideline goes on to state that confirmatory trials to demonstrate an effect on prevention of structural damage should be parallel group controlled trials of long duration. The observation period needed is not less than two years, showing sustained effects for the effects after the first year. With regard to the demonstration of maintenance of effect, it may be possible to extrapolate from the experience in related diseases such as RA. Consequently a shorter study should be justified taking into consideration the patient population and the natural course of development of joint damage. The guideline goes on to state that trials should be ideally double-blind, placebo-controlled trials but that the requirement for a long duration of a placebo-controlled trial may raise feasibility and ethical concerns. In the case of Study C0524T08, the observation period was two years. What concerned the Delegate was that it was difficult to obtain an accurate idea, from the data presented, of the extent of structural damage accruing from the natural history of the progression of the disease. There is only placebo-controlled data in this study out to 24 weeks at which point radiographs were taken. While this may appear a relatively short period, it is in fact in accordance with the guidelines which state that a period of placebo control of three to six months is acceptable. In the clinical evaluator's overall conclusions (see attached CER), there is a reference to a statistically significant mean change in the total vdH-S score from baseline to Week 24 for golimumab 50 mg compared with placebo ($p = 0.01$). Similar changes in the 100 mg group at week 24 did not achieve statistical significance. The 24 week data have been previously evaluated by the TGA for another application concerning Simponi: **the sponsor was requested to confirm this. The sponsor was also requested to integrate the analysis of data at 24 weeks with the analysis done at weeks 52 and 104 to determine what trends may be evident.**

There did not appear to be statistical tests of comparison applied to the data in this submission. That is why it is important to set the data in this submission in the context of the overall data, beginning with the placebo-controlled data at 24 weeks to which data statistical testing was applied.

In terms of the data that is to hand, as noted above, there is data in the dossier out to 104 weeks. From the upper half of Table 3, above, it can be observed that there is very little movement in the mean values of the scores in each of the groups, placebo, 50 mg, 100 mg and combined between baseline, week 52 or week 104. This relative lack of movement is also borne out by the results for the median scores and the interquartile ranges of scores for each time point. From the bottom half of the Table 3 at the changes from baseline at weeks 52 and 104, there is perhaps a suggestion of a more beneficial radiographic response in the 100 mg group compared with the 50 mg group with lesser, in fact more negative changes. It is also of interest and perhaps reassuring to note that when comparing the interquartile ranges for the change from baseline at week 52 with the corresponding ranges for the change from baseline at week 104, for each of the groups placebo, 50 mg and 100 mg, there is a slight shift to the left (along the number line) for the lower end of each of those interquartile ranges moving from week 52 to week 104. The upper ends of each interquartile range remain the same. Thus there does not appear to be any overall worsening of the total modified vdH-S score. Whether such an apparent benefit merits a specific indication is open to question. The Delegate had some concerns about this issue.

The sponsor was requested to submit its argument as to why the data does support a specific indication and also to clarify how the scope and detail of the data are in accord with the requirements of the relevant EU guideline. The sponsor was reminded of the Delegate's request for an integration of the data analyses at each of the 24-, 52- and 104-week timepoints.

The Delegate requested the sponsor perform a responder analysis of the change from baseline to weeks 52 and 104 in the total modified vdH-S score. The analysis is to show the percentages of patients at each of those time points who had a change from baseline in the total score of -5 or less (that is, -5 or more negative than -5), 0 or less, 5 or less, 10 or less and more than 10. The sponsor was also asked to give an analysis to show the percentages of patients at each of those time points whose change from baseline in the total score was x where x is defined by the following groups: $x \leq -10$, $-10 < x \leq -5$, $-5 < x \leq 0$, $0 < x \leq 5$, $5 < x \leq 10$, $10 < x \leq 15$ and $x > 15$.

Active rheumatoid arthritis

Study C0524T05 [GO-BEFORE]

This is an ongoing Phase III, multi-centre, randomised, double-blind, placebo-controlled, 4-arm trial of SC golimumab in MTX-naïve patients with active RA. 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 in combination with MTX. In addition, a golimumab 100 mg without MTX arm was also evaluated.

At Week 28, patients with <20% improvement from baseline in swollen and tender joint counts entered early escape 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 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. While the

radiographic report at Week 104 was not a pre-defined endpoint, it was nonetheless assessed and is the main criterion to support the proposed extension of indication. There were a number of secondary objectives.

Men and women aged 18 years or older were eligible to enrol if they had active RA for at least 3 months and had not received MTX therapy.

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 clinical evaluator states that 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. **The sponsor was requested to confirm whether or not statistically-based comparisons were made in the analysis of the radiographic data.**

The Delegate noted that later in the CER when results are reported they are accompanied by p-values, a fact which does suggest that statistical analyses were carried out. **The sponsor was requested to confirm if these analyses were carried out and, if so, give detailed comment on the statistical analysis plan for the radiographic outcomes including justifications for sample size and comments on whether the study was appropriately powered for any statistical comparisons which were made**. **The sponsor was also requested to give full details of the *a priori* change in the analysis population mentioned earlier, including details of the analysis population which was originally planned, that is, before the *a priori* change. The sponsor was further requested to justify the latter change.**

A total of 637 patients were randomised and 634 patients received at least one dose of study drug. 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.

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.

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). In the golimumab + MTX groups, ACR response rates achieved at Week 52 were maintained through Week 104.

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) (Table 4).

Table 4. Reporting of radiographic endpoints in Study C0524T05 (RA). Summary of change from baseline in total van der Heijde modified Sharp score at Week 52 stratified by screening CRP level; randomised subjects

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX		
			50 mg	100 mg	Combined
Subjects randomized	160	159	159	159	318
Change from baseline					
n	160	159	159	159	318
Mean ± SD	1.37 ± 4.555	1.25 ± 6.155	0.74 ± 5.233	0.07 ± 1.833	0.41 ± 3.929
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(0.00, 1.50)	(0.00, 1.00)	(-0.50, 0.50)	(0.00, 0.50)	(0.00, 0.50)
Range	(-9.0, 35.0)	(-8.0, 59.0)	(-12.4, 56.9)	(-8.5, 6.5)	(-12.4, 56.9)
p-value		0.266	0.015	0.025	0.006
Subjects with CRP < 1.5 mg/dL at screening					
n	83	80	82	82	164
Mean ± SD	0.98 ± 3.899	0.02 ± 2.036	0.07 ± 1.340	0.10 ± 1.169	0.08 ± 1.253
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(-0.50, 0.25)	(-0.50, 0.00)	(0.00, 0.50)	(-0.25, 0.25)
Range	(-2.5, 25.1)	(-8.0, 6.5)	(-3.0, 4.5)	(-5.0, 3.0)	(-5.0, 4.5)
Subjects with CRP ≥ 1.5 mg/dL at screening					
n	77	79	77	77	154
Mean ± SD	1.80 ± 5.163	2.50 ± 8.330	1.47 ± 7.348	0.04 ± 2.350	0.75 ± 5.485
Median	0.50	0.00	0.00	0.00	0.00
IQ range	(0.00, 2.00)	(0.00, 1.81)	(0.00, 0.91)	(0.00, 0.50)	(0.00, 0.70)
Range	(-9.0, 35.0)	(-4.0, 59.0)	(-12.4, 56.9)	(-8.5, 6.5)	(-12.4, 56.9)

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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). As noted earlier, there is a p-values cited in the context of 52 Week results which implies the existence of a statistical analysis plan. **The sponsor was requested to give the details of that plan.** The mean change from baseline values at Week 52 and Week 104 is shown in Table 5.

Table 5. Reporting of radiographic endpoints in Study C0524T05 (RA). Summary of change from baseline in total van der Heijde modified Sharp score at Week 52 and Week 104 (with imputation rules applied to all timepoints) stratified by screening CRP level; randomised subjects (Reading level 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)

a Includes subjects who early escaped at Week 28 or crossed over at Week 52 to receive golimumab 50 mg + MTX or dose escalated after Week 52 database lock to receive golimumab 100 mg + MTX.
b Includes subjects who early escaped at Week 28 to receive golimumab 100 mg + MTX or received MTX after Week 52 database lock.
c Includes subjects who early escaped at Week 28 or dose escalated after Week 52 database lock to receive golimumab 100 mg + MTX.
d Includes subjects who had at least one vdH-S score post Week 52.
e Missing imputation rules were applied.

Overall, the reductions from baseline to Week 52 in total vdH-S scores for the golimumab + MTX groups were small 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.

Results for other efficacy outcomes were supportive. Median improvements in ACR and CRP, DAS 28 responses, improvement in physical function as measured by change in the HAQ score and health related quality of life as measured by change in SF-36 were all maintained at week 104 in comparison with week 52.

Study C0524T06 (GO-FORWARD)

This is an on-going Phase III, 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 RA despite MTX therapy. In addition, a golimumab 100 mg without MTX arm was also evaluated. 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 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 were the effects of golimumab on ACR 20 response, and on structural damage at Week 104.

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.

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.

Improvement in radiographic imaging data at weeks 52 and 104 was counted amongst a number of other efficacy outcomes.

According to the CER, descriptive statistics were used to summarise most data. **The sponsor was requested to confirm whether or not statistically-based comparisons were made in the analysis of the radiographic data. If such analyses were carried out the sponsor was requested to give a detailed comment on the statistical analysis plan for the radiographic outcomes including justifications for sample size and comments on whether the study was appropriately powered for any statistical comparisons which were made.** Also the delegate noted that the radiographic endpoint was not a primary endpoint of the study. Indications, by their nature, should reflect the most robustly demonstrated findings of any study and these of course are the primary efficacy outcomes. **The sponsor was asked to justify why an endpoint classified among "other efficacy outcomes" should support an indication.**

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. 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.

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.

With regard to the results for the co-primary efficacy outcomes, the proportion of patients who had an ACR 20, ACR 50 or ACR 70 response was maintained from Week 52 through Week 104. 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.

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 Table 6.

Table 6. Reporting of radiographic outcomes in Study C0524T06 (RA). Summary of change from baseline in total van der Heijde modified Sharp score at Week 52 and Week 104 (with imputation rules applied to all timepoints); randomised 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]	106	108	83	69	152
Change from baseline at Week 52[e]					
n	105	106	81	66	147
Mean ± SD	2.31 ± 16.411	1.05 ± 3.402	0.37 ± 2.525	0.15 ± 1.797	0.27 ± 2.224
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(0.00, 1.00)	(0.00, 1.00)	(0.00, 0.50)	(-0.50, 0.50)	(-0.50, 0.50)
Range	(-9.0, 164.5)	(-2.5, 26.0)	(-11.3, 10.0)	(-4.5, 9.0)	(-11.3, 10.0)
Change from baseline at Week 104[e]					
n	106	108	83	69	152
Mean ± SD	2.59 ± 16.548	1.89 ± 5.731	0.36 ± 3.556	1.43 ± 10.325	0.84 ± 7.427
Median	0.00	0.00	0.00	0.00	0.00
IQ range	(0.00, 1.00)	(0.00, 1.08)	(-0.50, 0.50)	(-0.50, 1.00)	(-0.50, 0.51)
Range	(-10.0, 165.0)	(-3.0, 41.5)	(-11.5, 15.0)	(-7.5, 84.0)	(-11.5, 84.0)

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

Adapted from RE395 [E XRAY 79 CI, 10MAR2010 10:29

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 is shown in Table 7.

As shown in Table 6 above, the degree of worsening of the total van der Heijde modified Sharp score at weeks 52 and 104 does appear to be definitely less in the actively treated groups than in the placebo-treated (i.e. the group which commenced treatment with placebo). There is some uncertainty as to whether these differences are statistically significant as noted above. **The sponsor was asked to clarify this issue.**

Table 7. Reporting of radiographic outcomes in Study C0524T06 (RA). Number of subjects with no newly eroded joints and no new JSN at Week 104; randomised subjects by treatment regimen (Reading session 2)

		Golimumab		Golimumab + MTX		
	Placebo + MTX → Golimumab 50 mg + MTX	Golimumab 100 mg + Placebo Only	Golimumab 100 mg + Placebo → Golimumab 100 mg + MTX	50 mg Only	50 mg → 100 mg	100 mg
Randomized subjects by treatment regimen (Reading Session 2)[a]	77	37	71	48	64	69
Subjects with ≥ 1 uninvolved joint at baseline (erosion score of 0)[b]						
n	71	35	69	48	63	67
Subjects with no new erosions in the joints with a score of 0 at baseline	47 (66.2%)	22 (62.9%)	46 (66.7%)	35 (72.9%)	47 (74.6%)	49 (73.1%)

		Golimumab		Golimumab + MTX		
	Placebo + MTX → Golimumab 50 mg + MTX	Golimumab 100 mg + Placebo Only	Golimumab 100 mg + Placebo → Golimumab 100 mg + MTX	50 mg Only	50 mg → 100 mg	100 mg
Subjects with ≥ 1 uninvolved joint at baseline (JSN score of 0)						
n	71	35	69	48	63	67
Subjects with no new JSN in the joints with a score of 0 at baseline	56 (78.9%)	33 (94.3%)	58 (84.1%)	40 (83.3%)	51 (81.0%)	58 (86.6%)

[a] Includes subjects who had at least one score post Week 52.
[b] Exclude subjects with a missing score at Week 104.

With regard to the remainder of the "other efficacy outcomes", median percent improvement in CRP and ACR-N as well as the proportion of DAS28 (CRP) responders were all maintained from week 52 through week 104.

Study C0524T12 (GO-LIVE)

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/kg or 4 mg/kg given with or without MTX every 12 weeks, and placebo IV with MTX for a 48 week duration.

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, quality of life, PK, and the PD of IV golimumab. There were no radiological objectives in this study.

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.

The primary efficacy endpoint was ACR 50 response at week 14. There were a number of other efficacy endpoints including ACR20 & joint tenderness and swelling according to DAS28.

A total of 625 patients were planned and 643 patients were randomised into the study. All statistical tests were 2-sided and performed at α=0.05.

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.

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. 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%.

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).

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. Other efficacy outcomes were generally supportive.

Delegate's comments on radiographic findings of Studies C0524T05 and C0524T06 (studies on RA)

The total vdH-S score is an appropriate parameter to use when comparing radiographic outcomes. As noted in the relevant EU guideline, CPMP/EWP/556/95 rev 1/Final, for agents which are claimed to prevent structural joint damage, it is currently recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart ideally for 2 years using full randomisation and pre-agreed criteria. The placebo-control period of 24 weeks is in accord with the guideline. The critical need is to demonstrate sustained effects or maintenance of effect after the first year throughout the second year.

The Delegate has asked for comment from the sponsor (see above). The issues included the *a priori* change in the analysis population in Study C0524T05, the inclusion of the radiographic endpoint in Study C0524T06 amongst "other efficacy endpoints" and the statistical analysis plans for the radiographic findings in both studies. Although it would appear that there was only placebo-controlled data up to week 24 in both studies, the clinical evaluator does refer to a statistically significant result at week 52 in the Study C0524T05. **The sponsor was asked to clarify the whole issue of to what extent statistically-based comparisons were used in the RA studies. In doing so, the sponsor was requested to integrate the week 24 findings into the summary of findings at weeks 52 and 104 so that a more accurate view of the progression of those findings can be formed.**

Delegate's overall assessment on the radiographic findings of the three studies: Study C0524T08 (PsA) and Studies C0524T05 and C0524T06 (RA)

As noted in the CER, the level of evidence supporting a claim of inhibition of progression of structural damage is somewhat limited because of study design constraints. Importantly, there were no control groups in the PsA and RA studies from week 24 to week 104 and there are good ethical reasons for that. Furthermore, the results were confounded by withdrawals due to lack of efficacy, withdrawals due to AEs, early escape in non-

responding placebo patients and changes in concomitant medications amongst others. **It is critical that the sponsor, in its pre-ACPM response integrate the analysis of the findings at week 24 into the corresponding analysis for weeks 52 and 104.**

Certainly the data the Delegate has seen so far does not indicate any worsening of structural damage at week 104 in comparison with earlier time points but the Delegate questions whether this is sufficient evidence on which to make a claim for prevention or inhibition of structural damage. The difficulty is to ascertain precisely the natural history of progression of such damage in order to be able to factor the latter in to making any comparison. Clearly a lengthy placebo-control period where patients are knowingly exposed to the risk of structural damage would be ethically unacceptable. The guidelines advise that a placebo-control period of 3-6 months is acceptable. To a certain extent it has to be accepted that there will be damage accruing in the absence of treatment and an attempt has been made to make the best possible estimate of that damage. The critical question to be answered is has there been a real benefit or not and is the benefit sustained?

Safety

The safety data included pooled data for 3 different rheumatological indications, RA, PsA and AS as follows:

- The pivotal PsA Phase III SC Study C0524T08 (PsA)
- The pivotal RA Phase III SC Studies C0524T05, C0524T06, and C0524T11 including three subsets (MTX-naïve patients, MTX-experienced patients, and TNF-experienced patients).
- The combined Phase III SC studies for all rheumatologic indications: C0524T05 (RA), C0524T06 (RA), C0524T08 (PsA), C0524T09 (AS) and C0524T11 (RA)

There were also analyses separately evaluating safety data for the PsA and RA indications through weeks 100/104 as well as safety data from some non-pivotal efficacy studies in other, non-rheumatological indications.

In the Phase III studies of RA, PsA and AS (golimumab administered SC), 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 III 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.

Adverse events occurring in ≥5% of treated patients in the combined Phase III studies (RA, PsA and AS) through Week 100/104 are shown in Table 8. The proportions of patients who 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.

Table 8. Number of subjects with any adverse event (with frequency of ≥5% occurring in subjects receiving either golimumab dose) through Week 100/104 by MedDRA system organ class and preferred term; treated subjects in Phase III SC studies of RA, PsA and AS.

		Golimumab[a]		
	Placebo[b]	50 mg	100 mg	Combined
Treated subjects in Phase 3 SC studies of RA, PsA, AS[c]	639	1245	1377	2222
Avg duration of follow-up (weeks)	27.6	67.9	78.1	86.5
Avg exposure (number of administrations)	6.6	16.3	18.7	20.7
Subjects with any adverse events	469 (73.4%)	1033 (83.0%)	1137 (82.6%)	1985 (89.3%)
System-organ class/preferred term				
Infections and infestations	219 (34.3%)	690 (55.4%)	809 (58.8%)	1436 (64.6%)
Upper respiratory tract infection	56 (8.8%)	221 (17.8%)	266 (19.3%)	474 (21.3%)
Nasopharyngitis	42 (6.6%)	151 (12.1%)	176 (12.8%)	322 (14.5%)
Bronchitis	24 (3.8%)	93 (7.5%)	110 (8.0%)	202 (9.1%)
Sinusitis	15 (2.3%)	89 (7.1%)	94 (6.8%)	178 (8.0%)
Urinary tract infection	19 (3.0%)	56 (4.5%)	80 (5.8%)	132 (5.9%)
Gastrointestinal disorders	162 (25.4%)	395 (31.7%)	475 (34.5%)	848 (38.2%)
Nausea	51 (8.0%)	101 (8.1%)	138 (10.0%)	238 (10.7%)
Diarrhoea	37 (5.8%)	83 (6.7%)	102 (7.4%)	182 (8.2%)
Musculoskeletal and connective tissue disorders	133 (20.8%)	362 (29.1%)	458 (33.3%)	779 (35.1%)
Back pain	22 (3.4%)	87 (7.0%)	108 (7.8%)	194 (8.7%)
Arthralgia	29 (4.5%)	71 (5.7%)	98 (7.1%)	165 (7.4%)
Rheumatoid arthritis	24 (3.8%)	52 (4.2%)	76 (5.5%)	118 (5.3%)
General disorders and administration site conditions	95 (14.9%)	279 (22.4%)	364 (26.4%)	631 (28.4%)
Injection site erythema	7 (1.1%)	55 (4.4%)	109 (7.9%)	162 (7.3%)
Fatigue	25 (3.9%)	61 (4.9%)	90 (6.5%)	150 (6.8%)
Respiratory, thoracic and mediastinal disorders	91 (14.2%)	266 (21.4%)	288 (20.9%)	544 (24.5%)
Cough	37 (5.8%)	111 (8.9%)	122 (8.9%)	231 (10.4%)
Skin and subcutaneous tissue disorders	96 (15.0%)	245 (19.7%)	304 (22.1%)	538 (24.2%)
Rash	22 (3.4%)	51 (4.1%)	73 (5.3%)	122 (5.5%)

Table 8 continued. Number of subjects with any adverse event (with frequency of ≥5% occurring in subjects receiving either golimumab dose) through Week 100/104 by MedDRA system organ class and preferred term; treated subjects in Phase III SC studies of RA, PsA and AS.

		Golimumab[a]		
	Placebo[b]	50 mg	100 mg	Combined
Nervous system disorders	68 (10.6%)	240 (19.3%)	271 (19.7%)	504 (22.7%)
Headache	37 (5.8%)	106 (8.5%)	121 (8.8%)	226 (10.2%)
Investigations	70 (11.0%)	216 (17.3%)	231 (16.8%)	441 (19.8%)
Alanine aminotransferase increased	33 (5.2%)	101 (8.1%)	93 (6.8%)	192 (8.6%)
Aspartate aminotransferase increased	23 (3.6%)	72 (5.8%)	60 (4.4%)	131 (5.9%)
Injury, poisoning and procedural complications	53 (8.3%)	185 (14.9%)	237 (17.2%)	414 (18.6%)
Vascular disorders	30 (4.7%)	119 (9.6%)	163 (11.8%)	279 (12.6%)
Hypertension	16 (2.5%)	74 (5.9%)	103 (7.5%)	177 (8.0%)
Psychiatric disorders	34 (5.3%)	100 (8.0%)	128 (9.3%)	225 (10.1%)
Eye disorders	24 (3.8%)	95 (7.6%)	120 (8.7%)	213 (9.6%)
Metabolism and nutrition disorders	25 (3.9%)	71 (5.7%)	98 (7.1%)	167 (7.5%)
Blood and lymphatic system disorders	24 (3.8%)	66 (5.3%)	75 (5.4%)	141 (6.3%)
Reproductive system and breast disorders	19 (3.0%)	50 (4.0%)	72 (5.2%)	122 (5.5%)

[a] Prior to Week 100/104, received golimumab with or without MTX.
[b] Prior to Week 100/104, received placebo with or without MTX.
[c] C0524T05 (Week 104), C0524T06 (Week 104), C0524T11 (Week 100), C0524T08 (Week 104), and C0524T09 (Week 104). Subjects may appear in more than one column.

Infections of interest for the combined Phase III studies are shown in Table 9. 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 tuberculosis (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.

Table 9. Infections and infestations of interest occurring only in golimumab treatment groups in the combined Phase III SC studies in rheumatologic indications through Week 100/104 by MedDRA system organ class and preferred term.

		Golimumab[a]		
	Placebo[b]	50 mg	100 mg	Combined
Treated subjects in Phase 3 SC studies of RA, PsA, AS[c]	639	1245	1377	2222
Avg duration of follow-up (weeks)	27.6	67.9	78.1	86.5
Avg exposure (number of administrations)	6.6	16.3	18.7	20.7
System-organ class/preferred term				
Infections and infestations	219 (34.3%)	690 (55.4%)	809 (58.8%)	1436 (64.6%)
Sepsis	0 (0.0%)	1 (0.1%)	10 (0.7%)	11 (0.5%)
Pulmonary tuberculosis	0 (0.0%)	1 (0.1%)	6 (0.4%)	7 (0.3%)
Tuberculosis	0 (0.0%)	1 (0.1%)	2 (0.1%)	3 (0.1%)
Peritoneal tuberculosis	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)
Tuberculous pleurisy	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Histoplasmosis	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (0.1%)
Pneumonia legionella	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Septic shock	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)

[a] Prior to Week 100/104, received golimumab with or without MTX.
[b] Prior to Week 100/104, received placebo with or without MTX.
[c] C0524T05 (Week 104), C0524T06 (Week 104), C0524T11 (Week 100), C0524T08 (Week 104), and C0524T09 (Week 104). Subjects may appear in more than one column.

In the combined Phase IIb and Phase III 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.

There were no clinically meaningful differences between the AE profile for the pooled data and the AE profiles when separately considered for PsA and RA.

In the Phase III 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.

There were 16 deaths in the combined (RA, PsA and AS) studies of SC golimumab, and a further 5 deaths in the Phase III IV RA study. When all the rheumatologic Phase IIb and Phase III 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 IIb and Phase III rheumatologic studies, serious 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. 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).

There were no clinically meaningful differences in the SAE profiles in patients with PsA and RA when considered separately.

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).

There were no significant new safety signals arising from the laboratory test data.

Overall the Delegate agreed with the clinical evaluator that there were no new or unexpected safety signals which arose during the two year extension studies in RA or PsA.

First round risk-benefit balance

The clinical evaluator was of the opinion that 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 were considered to be adequately addressed in *Precautions* in the approved PI.

Second round clinical evaluation

Following the first round evaluation, the clinical evaluator asked two questions of the sponsor (see extract from the CER attached to this AusPAR). The first question was to do with the CRL issued by the US FDA to the US sponsor in relation to the evidence for the claim of inhibition of structural damage. The second was to do with the issue of dose linearity and whether it had been previously established. In the next section the Delegate will briefly canvass the issues raised in the questions.

The CRL issued by the US FDA stated the view that there was no substantial evidence to support the claims for radiographic response in both PsA and RA. The main concerns related to what were considered to be small but inconsistent changes in vdH-S scores with no long-term blinded, control data and to the fact that in Study C0524T05 statistically significant treatment benefits were demonstrated in the PP set but not in the ITT set. As

noted by the clinical evaluator, the critique of the US FDA is scientifically sound. However, the Delegate agreed with the sponsor that it is both unethical and impractical to conduct long-term placebo-controlled studies in patients with active disease.

Dose proportionality of golimumab was established during the evaluation of the original submission for registration.

The Delegate noted that following receipt of the second round CER, the sponsor clarified that no statistical comparisons with p-values were made after week 24 in the studies due to the lack of a placebo control arm.

Clinical evaluator's recommendation

The clinical evaluator has recommended that the extensions of indication sought by the sponsor should be approved.

The Delegate proposed that the recommendations of the clinical evaluator with respect to the PI revisions will be implemented. Details of these are beyond the scope of the AusPAR.

Risk Management Plan

No RMP was required to be submitted for this submission.

Risk-benefit analysis

Summary of issues raised by the Delegate

In the Overview, the Delegate has asked a number of questions concerning the data supporting the extension of indication in PsA. Broadly, these relate to the issues of placebo control and how account can be taken for the damage presumed to have occurred as a result of natural progression of the disease in patients in the placebo-control group. The extent and nature of all pre-defined statistically based comparisons relied upon in the submission and the scope and detail of the data are in accord with the requirements of the relevant EU guideline. Importantly the sponsor was requested to provide an overall integrated analysis of the data at each of the 24-, 52- and 104-week timepoints which demonstrates clearly why the data support the requested indication.

The sponsor has also been asked to carry out a number of post hoc responder analyses in relation to the data from Study C0524T08, the study in psoriatic arthritis.

The Delegate has asked a number of questions concerning the data supporting the extension of indication in RA. As with the data in PsA, these questions relate to the issues of placebo control and how account can be taken for the damage presumed to have occurred as a result of natural progression of the disease, that is, while the subject is in the placebo-control group, the extent and nature of all pre-defined statistically based comparisons relied upon in the submission and how the scope and detail of the data are in accord with the requirements of the relevant EU guideline. The Delegate has also requested the sponsor to provide an overall integrated analysis of the data at each of the 24-, 52- and 104-week timepoints which demonstrates clearly why the data support the requested indication.

Delegate considerations

The Delegate agreed with the clinical evaluator that a majority of patients maintained improvements of symptoms, physical function and inhibition of structural damage as shown by X-ray in the long-term extension studies of up to 2 years in PsA and RA.

The major problem with the claim for the inhibition of structural damage as shown by X-ray is that there is no placebo-controlled data after 24 weeks. However, the guidelines state that, depending on the severity and activity of the disease, a placebo control for three to six months is acceptable.

The sponsor has been asked to clarify a number of issues with regard to the data concerned with structural damage. Most critically, final approval will be contingent upon the sponsor's provision of satisfactory answers to all questions/requests in the Overview (highlighted above in bolded font), in particular the provision of analyses which integrate the placebo-controlled 24 week data (that is, data for which one can make statistically based comparisons) with the new 52 week and 104 week data.

The Delegate is satisfied that there is no evidence of worsening of the structural or radiological parameters at the later time points but was somewhat uncertain whether this occurred on a background of earlier improvements on active treatment. The Delegate acknowledged that the relevant study designs are necessarily complex largely because of valid ethical concerns about exposing patients to unnecessarily lengthy periods of placebo in a placebo control group.

The risks of golimumab are those shared by other anti-TNFα agents. No new or unexpected safety signals arose during the course of the evaluation of the safety data for this submission.

Proposed Action

The Delegate proposed to approve the submission for the indication below, based on the satisfactory establishment of safety and efficacy and for the reasons stated above under *Risk-Benefit Analysis*, if the sponsor provided acceptable clarifications and explanations for all matters raised in the Delegate's Overview.

Indication

The Delegate proposed to approve the following extension (text in bold) to the indication:

> *"Rheumatoid arthritis (RA)*
>
> *Simponi, in combination with methotrexate, is indicated for:*
>
> *The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate.* ***Simponi has also been shown to inhibit the progression of joint damage as shown by X-ray.***
>
> *Psoriatic arthritis (PsA)*
>
> *Simponi, alone or in combination with methotrexate, is indicated for:*
>
> *The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Simponi has also been shown to improve physical function* ***and to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.***
>
> *Ankylosing spondylitis (AS)*
>
> *Simponi is indicated for:*
>
> *The treatment of active ankylosing spondylitis in adult patients."*

This approval will be contingent upon the provision, by the sponsor, of satisfactory answers to all questions asked of the sponsor in the Overview and also upon amendment of the PI document[8] to the satisfaction of the TGA.

The Delegate intends to impose the following specific conditions of registration:

1. Post marketing reports are to be provided in line with the current published list of EU reference dates and frequency of submission of periodic safety update reports (PSURs) until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of periodic Safety Update Reports each covering six months.
2. the sponsor to provide to the TGA, as soon as available, the full final study reports of the studies listed below, these studies having been identified as ongoing at the time of writing the clinical evaluation report. The study reports are to be provided for formal evaluation by the TGA:
   - Study C0524T08 [GO-REVEAL]
   - Study C0524T05 [GO-BEFORE]
   - Study C0524T06 [GO-FORWARD]

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM, and requested advice and comment specifically with regards to the following issues:

a. Is the ACPM of the view that the sponsor has satisfactorily established the limitation or inhibition of structural damage conferred by active treatment in comparison with placebo treatment, firstly in the case of psoriatic arthritis and secondly in the case of rheumatoid arthritis? Is there for instance an accurate estimate, for each disease, of the degree of structural damage accruing from the natural history of progression of each disease or at least accruing from placebo treatment (other treatments being equal)? Because of ethical considerations, the duration of placebo control must be necessarily limited. The guidelines recommend that, depending on the severity and activity of the disease, three to six months is acceptable. Has the design of each study permitted an accurate assessment of the comparison between active and placebo in relation to the inhibition of structural damage?

b. The Delegate has requested the sponsor, in the response to the Delegate's Overview, provide clarification of the extent and nature of all pre-defined statistically based comparisons relied upon in seeking the extensions of indication and also to provide integrated analyses of the 24-, 52- and 104-week data which clearly demonstrate the benefit of golimumab in inhibiting the progression of structural damage in both psoriatic arthritis and rheumatoid arthritis. In both guidelines, that is, in those for PsA and RA there is a requirement that *"the observation period needed is not less than two years, showing sustained effects for the effects after the first year"*. Is the ACPM satisfied that the information supplied has resolved all concerns of the Delegate, in

[8] Details of discussion and revisions to the PI and CMI are beyond the scope of the AusPAR.

particular those concerns about the robustness of the data which demonstrates sustained effects after the first year? Are there further questions which should be asked of the sponsor in relation to the data?

Response from Sponsor

Product Information[9]

Indication

The sponsor agrees with the Delegate's recommendation to approve the extension of indications for Simponi; however, the sponsor does not agree with the indication text change proposed by the Delegate. The sponsor proposes to retain the following (extension shown underlined)

> *RA: Simponi, in combination with methotrexate, is indicated for:*
>
> *The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate.* ***Simponi has also been shown to inhibit the progression of structural damage.***
>
> *PsA: Simponi, alone or in combination with methotrexate, is indicated for:*
>
> *The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Simponi has also been shown to improve physical function* ***and to inhibit the progression of structural damage.***

For the RA indication extension, the Delegate recommended the following: *"Simponi has also been shown to inhibit the progression of joint damage as shown by X-ray,"* which is consistent with the EU SmPC wording for Simponi and with EU SmPCs for other TNF inhibitors. The sponsor does not agree with this wording because RA indications from other TNF inhibitors approved by the TGA do not stipulate "as shown by X-ray" even though their study designs stipulate radiographic changes. Furthermore, indications from other TNF inhibitors in Australia refer to "structural damage" in RA, rather than "joint damage." The sponsor requests that the RA indication for Simponi be consistent with indications for other TNF inhibitors in Australia. "

For the PsA indication wording, the Delegate recommended the following: *"Simponi has also been shown to improve physical function and to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease."* This text follows the EU SmPC text for Simponi and is consistent with EU SmPCs for other TNF inhibitors. However, it is not consistent with the indication wording for other TNF inhibitors in Australia, the US, or Canada, which reflect an indication for the broader PsA population. Furthermore, PsA Study C0524T08 was not restricted to polyarticular symmetrical subtypes (for details see section on *Psoriatic arthritis indication*, below). Therefore, the sponsor requests that the indication wording for Simponi be consistent with the labels for other TNF inhibitors in Australia and reflective of the patient population studied in the trial.

Efficacy: Comments by the Delegate common to PsA and AR indications

The Delegate has commented on issues regarding the extension to the PsA and RA indications.

[9] Note: matters relating to revisions to the PI outside of the *Indications* are beyond the scope of the AusPAR and therefore the sponsor's comments on these aspects are not included here.

Statistical analyses of the radiographic endpoints

The sponsor confirms that statistically based comparisons were made in the analysis of radiographic data at those time points for which a placebo-control group was present. The statistical analysis for the co-primary endpoint of change from baseline in modified vdH-S score at Week 24 (C0524T08) or Week 52 (C052T05) was pre-specified in the Statistical Analysis Plan (SAP) for each study; details are provided in the respective SAPS. No formal hypothesis testing was performed for data after the end of the placebo-controlled periods (that is, after Week 24 in C0524T08 or Week 52 in C0524T05).

Both studies were powered to detect significant treatment differences in reducing signs and symptoms of arthritis and inhibition of progression of structural damage (information on power calculations were provided in the SAPs). Study C0524T06 was not adequately powered to detect significant treatment differences in secondary endpoints, including the radiographic endpoint.

Studies C0524T05 and C0524T06 were both pivotal Phase III studies in subjects with RA. However, C0524T05 was designed as the primary study to measure radiographic efficacy, with a co-primary radiographic endpoint (versus a major secondary endpoint in C0524T06) and a longer placebo-controlled period than C0524T06 (52 weeks in C0524T05 versus 24 weeks in C0524T06). Consistent with the proposed PI, radiographic data from C0524T06 are not used to support the structural damage claim.

Integration of radiographic efficacy analyses at Weeks 24, 52, 104 and 6-month placebo-controlled period versus 2-year progression rate (Studies C0524T08 and C0524T05)

In both C0524T08 (PsA) and C0524T05 (RA), 2 different reading sessions were used through Week 104 in the evaluation of radiographic data. Reading Session 1 included images from baseline, Week 24, and Week 52 in C0524T08 and from baseline, Week 28, and Week 52 in C0524T05. In both studies, Reading Session 2 included images from baseline, Week 52, and Week 104. In each study, both sessions were read by the same 2 readers, but only Reading Session 1 used the adjudication process to support the primary endpoint (change from baseline in total modified vdH-S score). Scores from Reading Session 1 were not used for analyses based on Reading Session 2. In addition, analyses rules for Reading Session 1 in both studies differed from those for Reading Session 2. For these reasons, the 2 sessions should not be directly compared.

However, to assess trends for the primary studies supporting the PsA and RA structural damage indications, the mean change from baseline in total modified vdH-S scores for both Reading Sessions are presented for C0524T08 (PsA) at Weeks 24, 52, and 104 in Table 10 and for C0524T05 (RA) at Weeks 28, 52, and 104 in Table 11. In Reading Session 1, the results at Week 24/28 for the placebo group indicate the rate of progression of radiographic damage without golimumab treatment. The rate of progression in the golimumab groups was reduced compared with placebo through Week 24/28 and that reduction was maintained through Week 52. In Reading Session 2, the progression observed in the golimumab groups was similar at Week 52 and at Week 104, suggesting that the reduction in radiographic progression achieved at Week 24/28 was maintained through Week 104. Results are reported for Reading Session 1 in the C0524T08 and C0524T05 52-Week Clinical Study Reports (CSRs) and for Reading Session 2 in the C0524T08 104-Week CSR and in the C0524T05 104-Week CSR Addendum.

Table 10. Mean change from baseline in total van der Heijde Modified Sharp (vdH-S) score at Week 24, Week 52, and Week 104 (Reading Sessions 1 and 2); randomised subjects in C0524T08 (PsA)

Reading Session	Treatment group	Week 24	Week 52	Week 104
1	Placebo	0.27	0.22	
	Golimumab 50	-0.16	-0.22	
	Golimumab 100	-0.02	-0.14	
2	Placebo*		0.25	0.22
	Golimumab 50**		0.28	0.19
	Golimumab 100		-0.37	-0.33

* 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.

** Includes subjects who early escaped at Week 16 or dose escalated after Week 52 database lock to receive golimumab 100 mg.

Table 11. Mean change from baseline in total van der Heijde Modified Sharp (vdH-S) score at Week 28, Week 52, and Week 104 (Reading Sessions 1 and 2); randomised subjects in C0524T05 (RA)

Reading Session	Treatment group	Week 28	Week 52	Week 104
1	Placebo + MTX	1.11	1.37	
	Golimumab 50 + MTX	0.71	0.74	
	Golimumab 100 + MTX	0.01	0.07	
2	Placebo + MTX *		0.80	0.94
	Golimumab 50 + MTX **		0.06	-0.03
	Golimumab 100 + MTX		0.01	-0.20

* Includes subjects who early escaped at Week 28 or crossed over at Week 52 to receive golimumab 50 mg + MTX or dose escalated after Week 52 database lock to receive golimumab 100 mg + MTX.

** Includes subjects who early escaped at Week 28 or dose escalated after Week 52 database lock to receive golimumab 100 mg + MTX.

Because disease severity and the amount and rate of progression of joint damage are variable among RA and PsA patients there is not an established natural rate of radiographic progression for the patient populations. However, the amount of progression seen in the placebo group during the placebo-controlled period can be used to estimate the expected progression over 1 or 2 years without golimumab treatment. This likely underestimates what would have been the "natural" progression without any treatment, since in the golimumab PsA and RA studies, the placebo group was not a true placebo; that is, subjects (approximately half in C0524T08 and all in C0524T05) were receiving MTX, which is known to slow radiographic progression. The mean change from baseline in total vdH-S score in the placebo group in study C0524T08 at Week 24 was 0.27 (Table 10); using this rate, the expected change from baseline in total vdH-S score would be 0.54 at Week 52 and 1.08 at Week 104 if golimumab treatment were not given. The actual observed changes from baseline in total vdH-S score at Weeks 52 and 104 (Table 10) were substantially lower than these expected changes, indicating radiographic progression was inhibited with golimumab treatment long-term over 2 years. Similarly, in study C0524T05, the mean change from baseline in total vdH-S score in the placebo + MTX group at Week 52 was 1.37 (Table 11); using this rate, the expected change from baseline in total vdH-S score would be 2.74 at Week 104 if golimumab treatment were not given. The actual observed changes from baseline in total vdH-S score at Week 104 (Table 11) were substantially lower than this expected change.

Overall, these data are consistent in supporting the contention that golimumab treatment inhibits the progression of structural damage in both PsA and RA and that this effect is maintained through 2 years.

Scope and detail of the data in accord with the requirements of the EU guidelines

The sponsor is applying to add inhibition of progression of structural damage to the PsA and RA indications in the Australian label. Therefore, the focus of this application is to present radiographic data for the co-primary endpoint of change from baseline in total PsA-modified vdH-S score at Week 24 (C0524T08) and for the co-primary endpoint of change from baseline in total modified vdH-S score at Week 52 (C0524T05) for RA, which were performed to assess the ability of golimumab treatment to inhibit progression of structural damage compared with placebo. In addition, this application presents 104 week (2 year) data demonstrating the continued effect of golimumab on radiographic parameters.

The Delegate specifically requested the sponsor to clarify if the C0524T08 PsA Study was in accord with the requirements of the EU guidelines. The CHMP Guideline (CHMP/EWP/438/04, 2006) on clinical investigation of medicinal products for the treatment of PsA was considered in the development of the Phase III PsA study design in order to adequately assess the inhibition of progression of structural damage with Simponi. The vdH-S score, modified for the purpose of PsA radiological damage assessment by the addition cup and gross osteolysis abnormalities, was used to evaluate reduction of rate of progression of structural damage in study C0524T08. The vdH-S score is a validated radiographic measure and its PsA modification is accepted as a measure of structural damage progression in PsA by regulatory authorities and leading academic and community rheumatologists (CHMP/EWP/438/04, 2006; van der Heijde *et al*, 2005[10]; van der Heijde *et al*, 2007[11]; Antoni *et al*, 2008[12]). Furthermore, the assessed joints are in alignment with CHMP/EWP/438/04, 2006, *"Measure of Structural Joint Damage."* In addition, 2 year data demonstrating the continued effect of golimumab on inhibition of structural damage as provided for C0524T08 in this application, are in line with the EU Guideline (CHMP/EWP/438/04, 2006), *"Study Duration."* Furthermore, in accordance with the EU guideline, *"3.3.2. Additional claim to prevent structural damage,"* radiographic assessment and scoring in C0524T08 were done with 2 primary assessors blinded to patient, treatment, and sequence and the method for scoring and radiographic analyses followed pre-specified procedures.

Although similar clarification regarding the RA studies was not requested by the Delegate, it should be noted that the guidelines on clinical investigation of medicinal products for the treatment of RA (CPMP/EWP/556/95 rev 1/Final, 2003) were considered in the design of the RA trials. In accordance with this guidance, the change from baseline in the vdH-S score was used in C0524T05 to evaluate the co-primary endpoint of inhibition of progression of structural damage.

Efficacy: comments by the Delegate specific to PsA

Post hoc responder analyses

As requested, the sponsor has performed the following post hoc responder analyses for C0524T08 and detailed results are provided (not shown in this AusPAR).

- Percentage of patients who had a change from baseline in vdH-S score -5 or less, 0 or less, 5 or less, 10 or less and more than 10 at Week 52 and Week 104 (Reading Session 1 Week 24/52, Reading Session 2, Week 52/104)

[10] van der Heijde D, Sharp J, Wassenberg, Gladman D D. Psoriatic arthritis imaging: a review of scoring methods. *Ann Rheum Dis* 2005;64(supp II):ii61-ii64.
[11] van der Heijde DM, Kavanaugh, A, Gladmann DD, *et al*. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through 1 year of treatment: results from the induction and maintenance psoriatic arthritis clinical trial 2. *Arthritis Rheum* 2007;56(8):2698-2707.
[12] Antoni CE, Kavanaugh A, van der Heijde D, *et al*. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *J Rheumatol* 2008;35(5):869-876.

- Percentages of patients at each of those time points whose change from baseline in the total score was x where x is defined by the following groups:

  $x \leq -10$, $-10 < x \leq -5$, $-5 < x \leq 0$, $0 < x \leq 5$, $5 < x \leq 10$, $10 < x \leq 15$ and $x > 15$ (Reading Session 1, Week 24/52 and Reading Session 2, Week 52/104).

In Reading Session 1 in both analyses, a greater proportion of subjects in the golimumab groups evidenced no radiographic progression (change in vdH-S score ≤0) at Week 24 compared with subjects in the placebo group. These results were generally maintained through Week 52. In Reading Session 2, the proportions of subjects with no progression were maintained from Week 52 through Week 104 in both analyses. These findings are consistent with the results of the analyses for change from baseline in vdH-S score provided in the 52-Week and 104-Week C052T08 CSRs.

Clarification of PsA subtypes in study population

Inclusion criteria for C0524T08 specified that subjects must have at least 1 of the PsA subsets: distal interphalangeal (DIP) joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis. The study population enrolled reflects that diversity, with all subtypes represented.

Confirmation of previous TGA evaluation

The Sponsor confirms that the 24 week data were evaluated previously by the TGA.

Efficacy: comments by the Delegate specific to RA

A priori change in analysis population for Reading Session 2 in C0524T05

In the CSR of the C0524T05 SAP, it states that the analysis for change from baseline in total vdH-S score at Week 104 will be based on scores from Reading Session 2 and include subjects who had a total vdH-S score at either Week 52 or at Week 104. The purpose of this analysis was to evaluate the maintenance of inhibition of progression of structural damage through 2 years (104 weeks). The intention of this specification was to use data available at or after Week 52 for the Week 104 summary. However, specifying the use of scores at either Week 52 or at Week 104 did not take into account dropouts who might have a score at Week 52 but none after that. Therefore, in order to accomplish the original intention of the analysis (that is, evaluate data between Week 52 and Week 104), prior to the database lock for Reading Session 2 the Analysis Definition Rules were modified to specify that subjects must have at least 1 total vdH-S score after Week 52. This change had no impact on statistical testing since no formal hypothesis testing was performed based on these data.

Pharmacodynamics: comments by the Delegate

In Study C0524T14, there were clinically meaningful improvements in clinical assessments of disease activity (for example, DAS 28) but no meaningful statistical correlations between those clinical indices and serum biomarkers. The sponsor is requested to provide some comment on this issue.

As noted by the Delegate, C0524T14 was an open-label, Phase I study primarily designed to assess the PK of golimumab following multiple IV or SC administrations in subjects with RA. This study enrolled 49 subjects and was not powered to detect statistical correlations between clinical indices and serum biomarkers. An ACR 20 response was achieved by 62.1% of the 33 subjects who received SC golimumab injections and by 56.3% of the 16 subjects who received IV golimumab. Correlation analyses between biomarkers (baseline or change from baseline) and clinically relevant endpoints did not achieve statistical significance, but did trend as expected.

Conclusion

In summary, Simponi is considered effective in inhibiting the progression of structural damage in patients with PsA and RA and the sponsor agrees with the Delegate's recommendation to approve the extension of indications for Simponi, as proposed by the sponsor.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile for the extension of indications;

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

The ACPM advised that the evidence submitted was insufficient to support the extension of indications for PsA; however, had no objections to the PsA trial data being included in the PI. The trial data should include the statistical calculations supporting the radiological efficacy conclusions.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Simponi and Simponi SMARTJECT INJECTOR containing golimumab (rmc) for the new indications:

> ***Rheumatoid arthritis (RA)***
>
> *Simponi, in combination with methotrexate, is indicated for:*
>
> *The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including*

methotrexate, has been inadequate. Simponi has also been shown to inhibit the progression of joint damage as measured by X-ray.

Psoriatic arthritis (PsA)

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

The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Simponi has also been shown to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease, and improve physical function.

The full indications are now:

Rheumatoid arthritis (RA)

Simponi, in combination with methotrexate, is indicated for:

The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate. Simponi has also been shown to inhibit the progression of joint damage as measured by X-ray.

Psoriatic arthritis (PsA)

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

The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Simponi has also been shown to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease, and improve physical function.

Ankylosing spondylitis (AS)

Simponi is indicated for:

The treatment of active ankylosing spondylitis in adult patients.

Specific conditions of registration applying to these therapeutic goods

- The sponsor is required to implement the Risk Management Plan (RMP) as described in the document entitled 'Summary of the RMP' attached to the sponsor's e-mail to the TGA of 3 July 2013. The implementation of this RMP will continue until the approval of a new and/or amended RMP presently under evaluation as part of the submission PM-2013-00215-1-3.
- The sponsor must provide to the TGA, as soon as available, the full final clinical study reports of the studies listed below, these studies having been identified as ongoing at the time of writing the clinical evaluation report. The study reports are to be provided for formal evaluation within the context of category 1 submissions. The study reports required are those for the following studies:
  - Study C0524T08 [GO-REVEAL]
  - Study C0524T05 [GO-BEFORE]
  - Study C0524T06 [GO-FORWARD]

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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