Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Golimumab (rmc)

Proprietary Product Name: Simponi

Sponsor: Janssen Cilag Pty Ltd

June 2017

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 is responsible for regulating medicines and medical devices.
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- 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.
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- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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.

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Common abbreviations

Abbreviation	Meaning
ADR	adverse drug reaction
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
ASaT	All Subjects as Treated set
ASAS	Assessment in Spondyloarthritis International Society
ASDAS-C	Ankylosing Spondylitis Disease Activity Score CRP
ASQoL	Ankylosing Spondylitis Quality of Life Questionnaire
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
Axial SpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicines Information
CRP	C-reactive protein
CSR	Clinical Study Report
DMARDs	Disease-modifying anti-rheumatic drugs
ECLIA	electrochemiluminescent immunoassay
EMA	European Medicines Agency
EQ-5D	EuroQol-5D Health Questionnaire
EU	European Union
FAS	Full Analysis Set

Abbreviation	Meaning
GCP	Good Clinical Practice
GLM	Golimumab
HLA-B27	human leukocyte antigen B27
ICH	International Conference on Harmonisation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MRI	magnetic resonance imaging
NMSC	non-melanoma skin cancer
nr-Axial SpA	non-radiographic axial spondyloarthritis
NSAIDs	non-steroidal anti-inflammatory drugs
PD	pharmacodynamic
PI	Product Information
PK	pharmacokinetic
PLC	placebo
PsA	Psoriatic arthritis
PT(s)	Preferred Term(s)
RA	Rheumatoid arthritis
rmc	denotes production using recombinant mouse cells
SC	subcutaneous
SF-36	Short Form 36
SmPC	Summary of Product Characteristics
SPARCC	the Spondyloarthritis Research Consortium of Canada
TB	tuberculosis
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
TNF-α	tumour necrosis factor alpha
UC	ulcerative colitis
ULN	upper limit of normal
URTI	upper respiratory tract infection(s)
USA	United States of America
wk(s)	week(s)

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications
Decision:	Approved
Date of decision:	2 September 2016
Date of entry onto ARTG	9 September 2016
Active ingredient(s):	Golimumab (rmc)
Product name(s):	Simponi
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Road, Macquarie Park NSW 2113
Dose form(s):	Sterile Solution for Injection.
Strength(s):	50 mg of golimumab in 0.5 mL and 100 mg of golimumab in 1 mL
Container(s):	Pre-filled glass syringe with fixed stainless steel needle. This syringe is contained in a single-use pre-filled pen called 'SmartJect'.
Pack size(s):	1 or 3
Approved therapeutic use:	***Non-radiographic axial spondyloarthritis (nr-Axial SpAJ*** *Simponi is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSA/Ds).*
Route(s) of administration:	Subcutaneous (SC)
Dosage:	Non-radiographic axial spondyloarthritis: Simponi 50 mg given as a subcutaneous injection once a month, on the same date each month. Available data in non-radiographic axial spondyloarthiritis suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period
ARTG number (s):	153181, 153767, 208278 and 208279

Product background

This AusPAR describes the application by the sponsor to extend the indications of Simponi SmartJect Injector and the Simponi Pre-filled syringe containing 50 mg/0.5 mL or 100 mg/mL golimumab (rmc). The sponsor proposes to add a new sub-heading of 'Axial Spondyloarthritis' (AS) which will contain the existing AS indication and the proposed new indication of:

> ***Non-radiographic axial spondyloarthritis (nr-Axial SpA)***
>
> *Simponi is indicated for:*
>
> – *Reducing signs and symptoms*
> – *Improving spinal mobility*
> – *Improving physical function*
> – *Improving health related quality of life*
>
> *in adult patients with severe active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).*

Golimumab is a tumour necrosis factor alpha (TNF-α) inhibitor which is considered a key inflammatory mediator with a wide variety of functional activities. Abnormally high levels of TNF-α have been implicated in the pathophysiology of several immune-mediated diseases. Simponi is a human monoclonal antibody with an immunoglobulin G 1 heavy chain isotype (G1m [z] allotype) and a kappa light chain isotype. Simponi binds with high affinity to both soluble and transmembrane forms of TNF-α and inhibits TNF-α bioactivity.

The Assessment of SpondyloArthritis International Society (ASAS) classifies SpA with predominantly axial involvement into 2 groups:

a. AS, typically with radiographic sacroiliitis on plain radiography, and

b. nr-Axial SpA, axial SpA without plain radiographic changes of sacroiliitis.

While these conditions are often considered together, there remains some uncertainty regarding whether these categories represent distinct but overlapping disorders or simply different points in the severity or chronology of illness along a single spectrum. The sponsor provided an overview of axial spondyloarthritis and nr-Axial SpA (see *Clinical rational* below).

The currently approved indications in Australia are:

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.

Ulcerative colitis (UC)

Simponi is indicated for:

The treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy. Patients should show a clinical response within 6 weeks of treatment to continue treatment beyond that time (see CLINICAL TRIALS)

The standard dose approved for the rheumatology indications is 50 mg SC monthly and the proposed indication has the same dosage instructions. One other TNF inhibitor, etanercept, has been approved for the treatment of nr-Axial SpA in Australia. The initial management of nr-Axial SpA is with Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Other agents that have been used include local corticosteroid injections and Disease Modifying Antirheumatic Drugs (DMARDs), although the latter have not been shown to be effective for patients with purely axial disease and there is a lack of evidence for glucocorticoids in nr-Axial SpA.

Other members of the TNF-α inhibitor class registered in Australia include infliximab, etanercept, adalimumab and certolizumab pegol.

Current axial spondyloarthritis indications for these drugs are presented below:

Remicade

> *Ankylosing Spondylitis*
>
> *Remicade is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.*

Enbrel

> *Ankylosing Spondylitis*
>
> *The signs and symptoms of active ankylosing spondylitis in adults.*
>
> *Non-radiographic Axial Spondyloarthritis*
>
> *Treatment of adults with active* non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or MRI change who have had an inadequate response to NSAIDs.*
>
> **Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4.*

Humira

> *Ankylosing Spondylitis*
>
> *Humira is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.*

Cimzia

> *Ankylosing Spondylitis*
>
> *CIMZIA is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).*

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 13 November 2009.

At the time the TGA considered this application, Simponi had been approved in Europe (June 2015) and Canada (June 2016) for non-radiographic axial spondyloarthritis. It was under evaluation in Switzerland (submitted January 2015). The approved indications in Europe and Canada are as follows:

Europe

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

Canada

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

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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

Clinical rational

In the Clinical Overview the sponsor has described the submission clinical rationale as follows:

Axial spondyloarthritis (Axial SpA) is a chronic inflammatory disease of the axial skeleton typically manifested by chronic back pain, spinal inflammation, seropositivity for human leukocyte antigen (HLA)-B27, and extra-articular manifestations. Axial SpA encompasses both AS and non-radiographic axial spondyloarthritis (nr-Axial SpA), the latter of which includes patients with little to no changes in the sacroiliac joints on plain radiographs and thus do not meet modified New York criteria for AS. As a relevant subgroup of Axial SpA, the proportion of nr-Axial SpA amongst newly diagnosed patients is estimated to be between 20%-80% of all Axial SpA, depending on symptom duration, selection criteria, and other parameters, including availability of MRI.

Despite shorter disease duration, patients with nr-Axial SpA have substantial disease burden, similar to patients with AS, who have relatively longer disease duration. Data from the German GESPIC study and French DESIR study (in the nr-Axial SpA and AS groups, both with symptom duration of <5 years) report the same level of disease activity, as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and pain. Another study also notes no differences between the two groups with respect to other functional and quality of life measures, including the Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life questionnaire (ASQoL), and Short Form 36 (SF-36) health survey. Evidence that patients with nr-Axial SpA have the same level of disease activity and pain as patients with AS, and experience significant impact on their day to day and/or work-related activities, has also been observed in the cited study. The similar disease burden in patients with nr-Axial SpA who have disease features similar to patients with AS, but do not meet criteria for radiographic sacroiliitis as defined by the modified New York criteria, highlights the clear medical need.

Progression from nr-Axial SpA to AS occurs in approximately 10% of patients within the first 2 years from onset of symptoms and in approximately 60% of patients after 10 years. Based on current data, it does not appear that all patients with nr-Axial SpA progress to AS. Data suggest that the presence of MRI sacroiliitis and CRP elevation increase the likelihood of progression; in the presence of one or both of these factors, progression to AS is estimated to be approximately 20% within the first two years.

Guidance

The guidelines applicable to this submission are:

European Union (EU) Guidelines adopted by the TGA

- EMEA/CPMP/EWP/4891/03 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Effective: 23 February 2010.
- CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-Analyses; and 2. One Pivotal Study. Effective 27 March 2002.
- Australian regulatory guidelines for prescription medicines. Guidance 8: Product Information.

Although there is no specific EU Guideline for nr-Axial SpA, the Guideline relating to ankylosing spondylitis is relevant as it recognises that AS belongs to the group of spondyloarthritis (SpA) which includes psoriatic arthritis, arthritis/spondylitis with inflammatory bowel disease (IBD), reactive arthritis and undifferentiated SpA (patients with typical features of SpA that do not fulfil criteria for one of these subtypes).

The Assessment of SpondyloArthritis International Society (ASAS) has now classified SpA with predominantly axial involvement into 2 groups:

a. AS, typically with radiographic sacroiliitis on plain radiography, and

b. Axial SpA without plain radiographic changes of sacroiliitis (nr-Axial SpA).

While these conditions are often considered together, there remains some uncertainty regarding whether these categories represent distinct but overlapping disorders or simply different points in the severity or chronology of illness along a single spectrum.

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 pivotal efficacy/safety study (Protocol No. P07642, also known as MK-8259-006-02, and as GO AHEAD).
- An Integrated Summary of Safety and a report explaining the changes in ADR frequencies in the European Summary of Product Characteristics (SmPC).

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Study P07642 was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Pharmacokinetics

Studies providing pharmacokinetic data

The sponsor did not submit any pharmacokinetic studies. In the pivotal study (P07642), PK assessment was limited to the measurement of steady-state trough golimumab (GLM) concentrations at baseline and Week 16 before the administration of study medication. These were measured using the validated Meso Scale Discovery (MSD) electrochemiluminescent immunoassay (ECLIA). Immunogenicity of golimumab is discussed further in Attachment 2.

Evaluator's conclusions on pharmacokinetics

Median steady-state golimumab concentration after treatment with golimumab 50 mg SC every 4 weeks in nr-Axial SpA was 0.8 µg/mL. This compares with median steady-state trough serum concentrations in patients with AS of approximately 0.6 µg/mL (according to the currently approved Australian PI for Simponi) or 0.7 µg/mL (at Week 104 in Study C0524T09 when the same assay was used). The trend for lower serum golimumab concentrations in subjects with nr-Axial SpA weighing > 100 kg was also observed in population pharmacokinetic analyses for the other rheumatological indications. These findings support the proposed dosage and administration guidelines for nr-Axial SpA in the PI.

Pharmacodynamics

Studies providing pharmacodynamic data

The sponsor did not submit any pharmacodynamic studies. In the pivotal study (P07642), PD assessment was limited to the measurement of C-reactive protein (CRP) levels at baseline and Week 16.

Evaluator's conclusions on pharmacodynamics

Improvement in CRP levels in subjects with nr-Axial SpA receiving golimumab relative to placebo is consistent with improvement observed in the other rheumatological indications.

Dosage selection for the pivotal studies

Dose selection for the nr-Axial SpA indication was based on the currently approved dose for the treatment of AS and other rheumatologic diseases.

Given the similarity of the pathophysiology and clinical presentation of nr-Axial SpA and AS, and the comparability of golimumab exposure observed in clinical trials for both conditions, selection of the same dose is considered appropriate. This is also consistent with the approved dosing strategy for Enbrel, which has the same dose for both the AS and nr-Axial SpA indications.

Efficacy

Studies providing efficacy data

- 1 pivotal efficacy/safety study (Protocol No. P07642, also known as MK-8259-006-02, and as GO AHEAD).

Evaluator's conclusions on efficacy

The sponsor has provided data in the form of an interim study report from a single pivotal Phase IIIb study. Study P07642 was a two-part, randomised, double-blind, placebo-controlled study assessing the efficacy of golimumab in 197 subjects (97 on golimumab, 100 on PLC) aged 18 to 46 years who met the ASAS classification criteria for nr-Axial SpA. In Part 1 subjects received either golimumab 50 mg SC or placebo every 4 weeks for 16 weeks, while in Part 2 (open-label extension) all subjects received golimumab. The study is ongoing with data up to 24 weeks of treatment follow-up being included for evaluation. Given the number of shared clinical and genetic features between AS and nr-Axial SpA, it is considered that Study P07642 observed an adequate number of patients for an acceptable duration of time to assess efficacy and safety of golimumab in the nr-Axial SpA indication. Study design and conduct, choice of efficacy endpoints and statistical analyses were appropriate, and consistent with the relevant EU guideline.[1] While only a single study has been conducted, this is considered acceptable as it complies with the relevant EU Guideline.[2] In particular, the study has internal and external validity, the treatment effect is clinically relevant with a high degree of statistical significance ($p<0.0001$ for ASAS-20), the results were internally consistent within the majority of subgroups examined and

[1] CPMP/EWP/4891/03 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis
[2] CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study

across a large number of endpoints, and efficacy has previously been demonstrated for a similar disease (AS) (that is, the hypothesis tested is plausible).

The Week 16 analysis demonstrated that a statistically significantly greater proportion of subjects receiving golimumab achieved an ASAS-20 response compared with those receiving placebo (71.1% versus 40.0%, p<0.0001). Results were similar for the Per Protocol (PP) population, with an even greater difference in favour of golimumab observed in the Objective Signs of Inflammation (OSI) population (76.9% versus 37.5%, p<0.0001). The OSI (target) population is the population specified in the proposed indication for nr-Axial SpA for golimumab, and was added to the study after the Committee for Medicinal Products for Human Use (CHMP) required this subgroup (with baseline evidence of sacroiliitis on magnetic resonance imaging (MRI) and/or screening CRP level > upper limit of normal (ULN) to be specified in the nr-Axial SpA indication for Humira in September 2012. Significant effects favouring golimumab were also seen for the key secondary efficacy endpoints (Assessment in Spondyloarthritis International Society 40 (ASAS-40), Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI 50), ASAS Partial Remission, and the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI sacroiliac (SI) Joints Score) at Week 16 in each of the study populations, with a similar or greater magnitude of effect observed in the OSI population. Supportive analyses on numerous other secondary endpoints also favoured golimumab treatment, and subgroup analyses were generally consistent with the results observed in the overall population with the exception of the subgroup who had both a negative MRI and normal CRP at baseline, where there was no difference detected between the treatments.

Analyses were also performed up to Week 24 which showed a sustained clinical benefit for golimumab for each of the primary and key secondary endpoints during this period of follow-up. The final results of Study P07642 should be submitted for evaluation (proposed for November 2015 according to the Risk Management Plan (RMP)) to further characterise the long term benefit of golimumab for the treatment of nr-Axial SpA.

Overall, the data in this submission supports the efficacy of golimumab in the treatment of nr-Axial SpA.

Safety

Studies providing safety data

The following study provided evaluable safety data:

- Pivotal efficacy study (P07642)

The sponsor also presented comparative safety data from Study P07642 in nr -Axial SpA versus the combined AS studies dataset (Studies C0524T09 and C0524T29), the combined Phase III SC rheumatologic studies (AS, RA, and PsA) and compared to the overall dataset derived from studies of golimumab in other indications (AS, RA, PsA, UC and asthma). The sponsor's conclusion from comparing Adverse Events (AEs) in each of these datasets was that safety in the nr-Axial SpA population is comparable with the known safety profile of golimumab in the combined AS studies and in other rheumatological indications.

Otherwise, no further discussion of the comparative safety datasets is made. The evaluator is satisfied that the safety data from these datasets is consistent with what is presented in the currently approved Simponi PI and that based on a comparison of these data and the safety data from Study P07642 (discussed in Attachment 2), safety in the nr-Axial SpA population is comparable with the known safety profile of golimumab.

Patient exposure

At the time of the database lock, there were 97 subjects who were exposed to golimumab and 100 subjects exposed to placebo in Part 1, and 189 subjects exposed to golimumab in Part 2. In Part 1, the mean duration of exposure to golimumab and placebo was 109.4 days and 109.2 days, respectively (range 28 to 112 days for both treatments), with 96% subjects on each treatment having between 12 and 16 weeks exposure. In Part 2, the mean duration of exposure to golimumab was 288.4 days (range 56 to 364 days), with 162 subjects (86%) having between 32 and 52 weeks exposure, and 77 (40.7%) having between 48 and 52 weeks exposure.

Postmarketing data

There is no post-marketing golimumab data available in the proposed indication of nr-Axial SpA.

Evaluator's conclusions on safety

In the pivotal Study P07642, golimumab 50 mg in patients with nr-Axial SpA, golimumab was generally well tolerated. The overall incidence of AEs in Part 1 was slightly lower in subjects receiving golimumab than those receiving placebo (41.2% versus 47.0%, respectively), and this remained the case in Part 2 (39.8% versus 51.0%, respectively). The type and frequency of specific AEs was similar in both parts of the study and the AE profile was consistent with that seen with golimumab in AS and other inflammatory rheumatic diseases. Adverse drugs reactions were reported in 13.4% of subjects on golimumab and 17.0% of subjects on PLC. The most frequently reported adverse drug reactions (ADRs) were Infections and infestations, with nasopharyngitis being the most common single event (6 subjects, 3.0%). There were few serious AEs (SAEs) reported (3 in Part 1 [1 on golimumab] and 3 in Part 2), with only 2 events considered to be drug-related by the investigator (both in Part 2, 1 bacterial infection and 1 migraine). Discontinuations occurred in 3 subjects in Part 1: two on golimumab and one on PLC, with a further 3 subjects discontinuing during the golimumab open-label phase. Four subjects had antibodies detected but none had a hypersensitivity reaction, injection site reaction, or discontinued the study. There were no deaths reported and no reports of clinically important hepatobiliary events, serious opportunistic infections, tuberculosis (TB), or malignancies.

First round benefit-risk assessment

First round assessment of benefits

The benefits of golimumab in the proposed usage are:

- 71.1% of patients on golimumab achieved an ASAS-20 response rate at Week 16, compared with 40.0% on placebo. This comparison was statistically significant and clinically meaningful (difference in % versus placebo 31.2; 95% CI: 17.5, 43.6; p<0.0001). This difference was even higher in the OSI (target) population (difference in % versus placebo 39.6; 95% CI: 24.6, 52.6; p<0.0001)
- A significantly higher response on golimumab compared with placebo was also seen for the key secondary efficacy variables (ASAS-40 [56.7 versus 23.0%], BASDAI 50 [57.7 versus 30.0%], ASAS Partial Remission [33.0 versus 18.0%], and SPARCC MRI SI joints score [-5.3 versus -0.9]). Again, the difference in % versus placebo was even higher in the OSI (target) population.
- Efficacy was maintained up to Week 24.

- No new safety signals were identified. Safety in the nr-Axial SpA indication is supported by the safety findings in a large existing safety database in other inflammatory rheumatic diseases.

First round assessment of risks

The risks of golimumab in the proposed usage appear to be the same as those already identified in the Simponi PI for the existing indications, and include the potential for:

- Serious infections, serious opportunistic infections and TB
- Malignancies
- Serious hypersensitivity reactions
- Injection site reactions
- Antibodies to golimumab (which may reduce efficacy)

However, up to the data cut-off of May 6 for Study P07642:

- The overall incidence of AEs in both Part 1 and Part 2 of the study was slightly lower in subjects receiving golimumab than those receiving PLC.
- Few SAEs were reported, and only 5 subjects on golimumab withdrew because of an AE. While there were numerous infections reported, the percentage of subjects with one or more infections was similar in the golimumab and placebo groups, only 2 cases of serious infection were reported, and only one of these was considered drug-related. There were no deaths, serious hypersensitivity reactions, clinically important hepatobiliary events or malignancies reported and only 7 subjects (3 on PLC, 4 on golimumab) reported injection site reactions.
- While 4 subjects tested positive for antibodies to golimumab in Part 1 of the study, none of these subjects had a hypersensitivity reaction or discontinued the study, and antibody positivity did not appear to reduce efficacy.
- Efficacy and safety data are based on limited follow-up (24 weeks). The final results of Study P07642 should be submitted for evaluation (proposed for November 2015 according to the RMP) to further characterise the longer term benefit of golimumab for the treatment of nr-Axial SpA.

First round assessment of benefit-risk balance

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

First round recommendation regarding authorisation

It is recommended that the golimumab indications are extended to include non-radiographic axial spondyloarthritis subject to modification of the PI as described in Section 11.

The final results of Study P07642 should be submitted for evaluation (proposed for November 2015 according to the RMP) to further characterise the long term benefit of golimumab for the treatment of nr-Axial SpA.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to questions raised by the evaluator and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of golimumab in the proposed usage are largely unchanged from those identified in the First round. The exception is that efficacy has been shown to further improve out to Week 32, and to be maintained up to Week 52.

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of golimumab in the proposed usage are largely unchanged from those identified in the First round. Efficacy and safety results are now based on 52 and 60 weeks of data, respectively. No new safety signals identified in the final CSR.

Second round assessment of benefit-risk balance

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

Second round recommendation regarding authorisation

It is recommended that the golimumab indications are extended to include non-radiographic axial spondyloarthritis subject to modification of the PI (the details of the proposed PI modifications are beyond the scope of the AusPAR).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 11.4 (dated 14 May 2015, DLP 6 May 2014) with Australian Specific Annex (ASA) Version 4.0 (dated 13 July 2015)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 1.

Summary – Ongoing Safety Concerns	
Important identified risks	Serious infections including opportunistic infections and TB
	Demyelinating disorders
	Hypertension

Summary – Ongoing Safety Concerns	
	Lymphoma (excluding HSTCL)
	Hepatitis B virus reactivation
	Congestive heart failure
	Autoimmune processes
	Haematologic reactions
	Serious systemic hypersensitivity (including anaphylactic reaction)
	Vasculitis
	Psoriasis (new onset or worsening of pre-existing)
	Skin cancer
Important potential risks	Malignancy
	Serious hepatotoxicity
	Exposure during pregnancy
	Serum sickness
	Maladministration/administration error
	Serious depression including suicidality
	Sarcoidosis/sarcoid-like reaction
	Colon cancer/dysplasia (in UC)
	HSTCL
	Medication error (wrong dose related to different strengths)
Missing information	Use in paediatric patients
	Use in patients with hepatic impairment
	Use in patients with renal impairment
	Use in patients with a past history of latent or active TB
	Use in patients with concurrent malignancy or a history of malignancy
	Use in patients with active infection including HIV, hepatitis

Summary – Ongoing Safety Concerns	
	B, hepatitis C
	Use in patients with recent prior use of other biologics excluding anti-TNFα agents
	Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF
	Use in patients with a history of demyelinating disease
	Use in patients with a history of lupus or lupus-like syndrome
	Use in patients after recent vaccination with live bacterial or viral vaccine
	Long-term safety data

Pharmacovigilance plan

The sponsor proposes routine and additional (which include a follow-up questionnaire and trials, registries and epidemiology studies) pharmacovigilance activities for all safety concerns and missing information.

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities for Australia.

The following additional activities are also proposed for Australia:

- An educational program is proposed for the safety concern of serious systemic hypersensitivity (including anaphylactic reaction), skin cancer, serum sickness, and maladministration/administration error.

Also indicated in the ASA, the educational program includes the following for target audiences:

- Company medical and commercial personnel*:* prepare and implement training programmes with training slides.
- Health Care Professionals (HCPs)*:*
  - Include Simponi information in relevant speaker training sessions, physician training programmes and other educational venues.
  - On-request availability of Medical Information related to Simponi.
  - Provide a training device and injection instructions which are available in a variety of different mediums to relevant HCPs for appropriate distribution to patients.
  - Educational material covering key safety concerns.
- Patients:
  - Patient kit containing information booklet outlining the profile of the product, key safety information and instructions for use of Simponi including storage is available for patients via the physician. Patients are also provided an opportunity to enrol in a patient support program.

- Simply for Me Patient Support Program (PSP) consists of:
  - Nurse support by a team of trained and qualified nurses providing correct self-injecting technique, including patient self-care and expectation after each self-injection.
  - Medication reminder service providing an SMS, email or phone call to patients prescribed Simponi to remind them of their next dose.
  - An education resource for patients describing the relevant disease state, information on how to store and how to inject Simponi, safety information, as well as the Consumer Medicine Information (CMI).
  - On-request availability of Medical Information related to Simponi.

It is noted in the ASA that the sponsor has advised that a Patient Alert Card (PAC) (proposed in the EU) will not be used in Australia.

Reconciliation of issues outlined in the RMP report

Table 2 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.'

Table 2: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	***Sponsor's response (or summary of the response)***	**RMP evaluator's comment**
Recommendation 1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*Sponsor response: The sponsor committed to considering any issues raised in the Clinical Evaluation Report.*	No issues were raised in the Clinical Evaluation Report. Therefore no further action was required by the sponsor.
Recommendation 2. According to the EU RMP, the final report for Study C0524T18 is anticipated for February 2016 whereas the ASA identifies the final report being anticipated for July 2015 with a submission date for Australia as September 2015.The dates relating to the completion and reporting of Study C0524T18 should be corrected in the next RMP/ASA submission.	*Sponsor response: The ASA has been updated and is included with this response. The dates relating to the completion and reporting of Study C0524T18 have been*	The date has been updated in the ASA to February 2016 and the study is reported as complete. The sponsor is reminded that the results of pharmacovigilance activities should be reported to the TGA in

Recommendation in RMP evaluation report	*Sponsor's response (or summary of the response)*	RMP evaluator's comment
corrected in this version of the ASA.		an appropriate and timely manner.
Recommendation 3. It is noted that the educational material provided in the RMP at Annex 11 is that of the EU, referring to the PAC which is not being provided in Australia. The educational material at Annex 11 also does not mention any change related to this application, being the extension of indications to include nr-Axial SpA. Updated materials should be provided to the TGA as relevant for Australia.	*Sponsor response: Janssen will update the Australian PI (AU PI), CMI and HCP booklets on approval of the nr-Axial SpA indication for Simponi.* *Annex 10 of the RMP provides details of the Additional Risk Minimisation Activities, and Janssen added 'nr-Axial SpA' as part of the RMP version update associated with the approval of the indication. Therefore, the use of current educational materials has been extended to HCPs prescribing Simponi for nr-Axial SpA. Mock-ups for the educational materials were not available at the time of nr-Axial SpA submission in the EU.*	Draft Australian educational materials have been provided. The sponsor should indicate how the Australian educational materials will change with the proposed extension of indications.
Recommendation 4. The approved EU Summary of Product Characteristics (SmPC) and proposed PI have been reviewed for their consistency. Advice relating to the safety concerns is considered to be generally equivalent in intent from a RMP perspective. However, it is noted that there are some differences in the text advice provided for, but not limited to, the following (based on proposed PI and SmPC for 50 mg solution for injection in pre-filled pen): Precautions relating to tuberculosis, hepatitis B reactivation, paediatric malignancy, lymphoma and leukaemia, colon dysplasia/carcinoma. Given the differences observed, and in accordance with the RMP guidance, the sponsor should provide a table in the ASA which compares differences (and provides reasoning for such differences) between the risk minimisation advice of the SmPC and PI. Instructions for doing so can be found in the TGA guidance at http://www.tga.gov.au/book/australian-specific-annex-template.	*Sponsor response: Janssen has included a summary comparison table of the EU SmPC and AU PI text in an*	A table has been added in Appendix 5 of the ASA which compares the EU SmPC and Australian PI statements. However, this table should include the exact wording as stated in the TGA guidance.

Recommendation in RMP evaluation report	*Sponsor's response (or summary of the response)*	RMP evaluator's comment
updated version of the ASA to the EU-RMP which is included with this response.		
Recommendation 5. In addition, the SmPC includes the following precaution relating to potential for medication error: *Potential for medication error: Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.* The Delegate may wish to consider whether a similar precaution should be explicitly provided in the PI.		This recommendation will be retained for the Delegate to consider.
Sponsor response: Janssen acknowledges the RMP Evaluator's comments and awaits the Delegate's advice on whether additional statements on the potential for medication error are required. *Note to Evaluator: As the EU-RMP v15.0 has recently become available and Janssen has taken this opportunity to provide this version and has updated the ASA in line with this version.*		

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

A number of recommendations were not adequately addressed by the sponsor. It is noted that these issues are of relatively minor consequence and the incorporation of these changes into the next scheduled update of the EU-RMP/ASA would be acceptable. The following issues should be addressed:

- **Recommendation 2**. The sponsor has indicated that Study C0524T18 was completed in February 2016, with results incorporated into the EU-RMP version 15.0. The sponsor is reminded that the results of pharmacovigilance activities should be reported to the TGA in an appropriate and timely manner (for example through Periodic Safety Update Report (PSUR) reporting or as a Safety Related Request).
- **Recommendation 3**. The sponsor should indicate how the draft educational materials for HCPs and patients will be modified to include the proposed indication. If golimumab is approved for the proposed indication, the revised educational material should be included as an attachment to the updated ASA.

- **Recommendation 4**. The sponsor should modify the table in Appendix 5 of ASA to include the exact wording of the EU SmPC and Australian PI as indicated in the TGA ASA template.
- **Recommendation 5**. The EU SmPC includes a precaution for 'Potential for medication errors' without a corresponding warning in the Australian PI. The Delegate should consider whether a similar warning should be included in the Australian PI.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

EU-RMP Version 11.4 (dated 14 May 2015, Data Lock Point 6 May 2014) with Australian Specific Annex (ASA) Version 4.0 (dated 13 July 2015) has been superseded by:

EU-RMP Version 15.0 (dated 2 February 2016, DLP 6 October 2015) and Australian Specific Annex Version 4.1 (dated 29 March 2016), which has incorporated the sponsor's response to the TGA's requests. Key changes from the version evaluated in the first round evaluation are summarised below:

Summary of key changes between EU-RMP versions 11.4 and 15.0, and ASA versions 4.0 and 4.1.	
Indications	Polyarticular juvenile idiopathic arthritis added as a proposed indication (EU)
Safety specification	'Sarcoidosis/sarcoid-like reaction' changed from a potential risk to an identified risk. 'Leukaemia' added as an important identified risk Description of safety concerns due to missing information changed from 'use in paediatric patients' to 'use in paediatric patients with ulcerative colitis'.[3] 'Long term safety in paediatrics' added as new missing information.[3] Description of missing information changed from 'Long term safety' to 'Long term safety in adults'.[3]
Pharmacovigilance activities	Study CNTO148UCO1001 added as an additional PV activity Updated with study MK-8259-050 to include all important identified and potential safety concerns with the exception of colon cancer/dysplasia (in ulcerative colitis).[4] Added JIA registry as additional PV activity.[4] Submission of final clinical study reports of Phase 3 UC clinical study C0524T18 (category 3) and Phase 3 nr- Axial SpA clinical study P07642 (category 4).
Risk minimisation activities	Updated to include wording on medication error.

[3] These changes are listed in Table 10 on p 404, but have not been included in the Summary of Safety Concerns table on p 273 [pages and tables referred to are not in this AusPAR].
[4] This change does not appear to have been implemented in the EU-RMP.

Summary of key changes between EU-RMP versions 11.4 and 15.0, and ASA versions 4.0 and 4.1.	
ASA	'Leukaemia' added as an important identified risk. 'Sarcoidosis/sarcoid-like reaction' updated from important potential risk to an important identified risk. Minor editorial changes to align with EU-RMP v15.0 History of submission for EU RMP 11.4 added Table of studies in Pharmacovigilance plan updated with revised dates, and Study C0524T18 removed from Table 4 (current studies) as it has been completed Risk minimisation section updated to refer to Appendix 1 (printed educational material for HCPs) Appendix 5 added which compares wording in SmPC with PI Questionnaire in Appendix 3 updated with 2016 date

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

Some of the changes in the EU-RMP do not relate to Australia as the polyarticular juvenile idiopathic arthritis indication has not been sought here. In addition, some of the changes listed in the *Summary of Changes to the Risk Management Plan over Time* have not been implemented in the revised EU-RMP (see footnotes 3 and 4).

In summary, while the proposed changes are considered acceptable, the quality of the revised EU-RMP and ASA should be addressed by the sponsor.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- EU-RMP Version 15.0 (dated 2 February 2016, DLP 6 October 2015) and Australian Specific Annex Version 4.1 (dated 29 March 2016), to be revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

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

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

The clinical evaluator has recommended approval for the proposed indication.

Pharmacokinetics

Median steady-state golimumab concentration after treatment with golimumab 50 mg SC every 4 weeks in nr-Axial SpA was 0.8 μg/mL which was comparable to the median steady-state trough serum concentrations in patients with AS of approximately 0.6 μg/mL (PI) or 0.7 μg/mL (at Week 104 in Study C0524T09 when the same assay was used). A trend for lower serum golimumab concentrations in subjects with nr-Axial SpA weighing > 100 kg was seen which was also observed in population pharmacokinetic analyses for the other rheumatological indications. At Week 52, the median golimumab concentration was 0.8 μg/mL.

Pharmacodynamics

A significantly greater reduction in CRP at Week 16 was seen in subjects in the golimumab 50 mg group than in the placebo group (-0.99 mg/dL versus -0.35 mg/dL, respectively; p=0.0003).

Efficacy

Dose selection for the nr-Axial SpA indication was based on the currently approved dose for the treatment of AS and other rheumatologic diseases which is considered acceptable given the overlap between AS and nr-Axial SpA.

Study P07642 (GO-AHEAD): This was a Phase IIIb, multinational, multicentre, two-part, randomised, double-blind, placebo-controlled study of 50 mg SC every 4 weeks of golimumab in 198 subjects with nr-Axial SpA. The study had a double blind placebo controlled period of 16 weeks followed by an open label extension of 44 weeks in which everyone received golimumab 50 mg.

The sponsor initially submitted data up to Week 24 but provided the full study report to Week 60 during the second round of evaluation.

Background NSAIDs were permitted. Males and females aged 18 to 45 years with a physician's diagnosis of active Axial SpA with disease duration ≤ 5 years, chronic back pain ≥ 3 months duration, and an inadequate response or intolerance to NSAIDs were eligible and in addition each subject had to meet one of two criteria adopted from the Assessment in Spondyloarthritis International Society (ASAS) for diagnosis of SpA. These criteria included active inflammation on MRI highly suggestive of sacroiliitis associated with spondyloarthropathy (as evidenced by the central reader) and 1 or more spondyloarthritis characteristics or HLA-B27+ gene and 2 or more spondyloarthritis characteristics.

The spondyloarthritis characteristics included inflammatory back pain, elevated CRP, arthritis and family history of SpA amongst others. Patients were excluded if they had bilateral sacroiliitis Grade 2 or unilateral sacroiliitis Grade 3 or Grade 4 on conventional X-rays (that is, excluding New York modified criteria for diagnosis of AS). To determine if patients had AS, 82% had x-rays taken within 30 days of screening and the remainder had them up to 71 days of screening.

Randomisation was stratified by evidence of sacroiliitis on MRI and CRP level and the protocol was subsequently amended to ensure that subjects had active inflammation at study entry. X-rays and MRIs were read centrally by readers blinded to treatment assignment, clinical information, and results of investigator readings. An analysis population was added prior to unblinding called the OSI Population which is a subset of the full analysis set and consisted of subjects with baseline evidence of sacroiliitis on MRI and/or screening CRP level >ULN. Study completion rate was 88.9% at Week 52.

Baseline demographics and disease characteristics were similar between golimumab and placebo groups (male 57.1%, median 30 years of age, 100% White, 67% having a disease duration < 1 year, 82% HLA-B27 positive, > 50% had failed ≥ 2 prior NSAIDs, 41% elevated CRP, 67% evidence of sacroiliitis on MRI, mean BASDAI score of 6.6 cm and 6.4 cm, 87.6% versus 83.0% on anti-inflammatory/anti-rheumatic product) except gender (male 62.2% versus 52%). In the OSI population the baseline demographics and disease characteristics were similar to those seen in the FAS population with the exception of those characteristics related to the definition of the OSI population (CRP >ULN in 51%, 83% evidence of MRI sacroiliitis and 33.5% had both).

The primary efficacy endpoint which was the proportion of subjects who achieved an ASAS-20 response at Week 16 for golimumab versus placebo using the final analysis set, was significantly higher on golimumab (71.1%) versus placebo (40.0%), with a difference of 31.2% (95%CI 17.5-43.6; p<0.0001). The PP analysis showed similar results. The OSI population result was similar at 76.9% on golimumab versus 37.5% on placebo, a difference of 39.6% (95% CI: 24.6, 52.6; p<0.0001). Key secondary endpoints, Full Analysis Set (FAS), were significantly higher on golimumab versus placebo for the ASAS-40 (56.7 versus 23.0%), BASDAI 50 (57.7 versus 30.0%), and ASAS Partial Remission (33.0 versus 18.0%) endpoints. A significantly greater reduction from baseline in the SPARCC MRI SI joints score was seen on golimumab versus placebo (-5.3 versus -0.9, respectively; p<0.0001). Similar results were seen for the OSI population. Four subjects developed antibodies but all achieved an ASAS-20.

Examining the subgroups for ASAS-20 response at Week 16, it was noted that the subgroup that had both a negative MRI and normal CRP at baseline had no difference detected between golimumab and placebo whereas the other combinations did as shown below. Female response rates showed a smaller treatment difference than was expected, which may have been at least partially due to a higher proportion of female than male subjects with a CRP within the normal limits (77% versus 46%, respectively). In the OSI population, which excluded those subjects with both a negative MRI and a CRP ≤ ULN, ASAS response was lower in females than males.

Table 3: Subgroup Analysis of Subjects Achieving ASAS 20 Response at Week 16 by Baseline MRI and Screening CRP (FAS, Part 1)

Baseline MRI sacroiliitis (+) and Screening CRP ≤ upper limit of normal				
GLM 50 mg	26 /39	66.7	28.2 (5.9, 47.8)	0.0132
Placebo	15 /39	38.5		
Baseline MRI sacroiliitis (+) and Screening CRP >upper limit of normal				
GLM 50 mg	22 /26	84.6	47.6 (21.9, 67.2)	0.0005
Placebo	10 /27	37.0		
Baseline MRI sacroiliitis (-) and Screening CRP ≤ upper limit of normal				
GLM 50 mg	9 /19	47.4	-2.6 (-32.7, 27.9)	0.8711
Placebo	10 /20	50.0		
Baseline MRI sacroiliitis (-) and Screening CRP >upper limit of normal				
GLM 50 mg	12 /13	92.3	56.6 (21.3, 79.2)	0.0028
Placebo	5 /14	35.7		

‡ Derived based on the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes or no) and screening CRP level (≤ upper limit of normal or > upper limit of normal) as stratification factors.

In the extension phase, efficacy (as measured by the primary and key secondary efficacy endpoints) that was observed with golimumab treatment at Week 16 was maintained out to Week 52. Results in the OSI population were consistent with those in the FAS population. Reduction in CRP from baseline was relatively stable between Week 24 (-1.02 mg/dL) and Week 52 (-1.15 mg/dL). In the placebo switch to golimumab group at Week 16, a marked improvement in efficacy response was observed between Week 16 and Week 20 and the response remained relatively stable thereafter. Of the 14 subjects who were positive for antibodies to golimumab, 8 achieved ASAS 20 at Week 52, 4 did not achieve ASAS 20 at Week 52, and 2 terminated early.

Safety

Exposure to golimumab in the pivotal study occurred in 97 subjects during the controlled period and 189 subjects were exposed during the open label extension period (mean 297 days) with 83 patients exposed between 48 and 52 weeks. Comparing golimumab with placebo during the controlled period, AEs occurred in 41.2% versus 47.0% with the most common categories being Infections and infestations, Gastrointestinal disorders and Nervous system disorders. The most common AEs were: nasopharyngitis (9.3% versus 9.0%), headache (7.2% versus 6.0%), nausea (6% placebo), oropharyngeal pain (5.2% golimumab), and influenza (5% placebo). Most events (89%) were mild to moderate. ADRs occurred in 13.4% versus 17%, with infections/infestations being most common (9.3% versus 7%). No deaths were reported and one unrelated SAE was reported. Discontinuations were low. No malignancies, clinically important hepatobiliary events, serious infections or serious hypersensitivity reactions were reported. Injections site reactions occurred in 3 placebo patients. Four subjects were antibody positive (all neutralising).

In the extension period, there was no new safety signals observed. AEs occurred slightly less in those who stayed on golimumab versus the switch group (41.9% and 54.2%). The most common AEs for those who stayed on golimumab were: nasopharyngitis (5.4%), influenza (2.2%), headache (6.5%), and upper respiratory tract infection (URTI) (4.3%). Most events (94%) were mild to moderate. ADRs occurred at a similar rate to the controlled period at 12.9%, with Infections and infestations being most common (10.8%). No deaths were reported in the extension and five SAEs were noted (2 related of migraine and bacterial infection). Discontinuations were low. No malignancies, clinically important hepatobiliary events or serious hypersensitivity reactions were reported. Two serious infections were reported. Injections site reactions occurred in 4 patients. Fourteen

subjects were antibody positive (all neutralising). There were few additional adverse events reported in the final CSR, with no new safety signals identified in patients with nr-Axial SpA.

Three subjects on golimumab had an alanine aminotransferase (ALT) ≥ 3x ULN and no subjects had an aspartate aminotransferase (AST) ≥ 3x ULN after baseline. Haematological abnormalities were noted, for example neutropenia and lymphopenia.

Risk management plan

The TGA has accepted the EU Risk Management Plan for Simponi (golimumab), version 15.0 (dated 2 February 2016, DLP 6 October 2015), with the Australian Specific Annex, version 4.1 (dated 29 March 2016) and any future updates as a condition of registration.

There were a number of relatively minor recommendations whose incorporation into the next scheduled update of the EU-RMP/ASA would be acceptable. The sponsor has provided assurances to address them, which the RMP evaluator has accepted.

The following outstanding matters should be followed up by the sponsor with the RMP evaluator and in the Pre-Advisory Committee on Prescription Medicines (ACPM) Response where required:

a. Statement on potential for medication errors in the EU SmPC. The sponsor should explain why it was included in the EU SmPC and whether this was based on reports of medication errors.

Risk-benefit analysis

Efficacy

The efficacy of golimumab in patients with nr-Axial-SpA has been satisfactorily demonstrated up to Week 16 in a single pivotal study and was maintained in the open label extension phase of the study up to Week 52. The proposed dose is the same as for other approved rheumatological indications and although there is no specific EU guideline on nr-Axial- SpA, the design and duration of the study is broadly consistent with the EU guideline on ankylosing spondylitis. The primary efficacy endpoint is considered an acceptable and validated endpoint in ankylosing spondylitis and therefore reasonable to use in nr-Axial-SpA and whilst the secondary endpoints are mostly commonly used, only the four key secondary endpoints were adjusted for multiplicity effects and not the numerous other endpoints which are therefore of descriptive nature only. ASAS-40 rather than 20 is considered a preferable primary endpoint in an ankylosing spondylitis population and although this was a secondary endpoint in this study, it demonstrated a statistically significant result. There is a potential for misclassification of patients with ankylosing spondylitis in this relatively newly recognised clinical entity of nr-axSpA and the use of historical x-rays at screening could add to this misclassification. However x-rays (and MRIs) were read centrally in a blinded manner and at screening 82% had x-rays within 30 days of screening which is considered acceptable given the slow rate of disease progression.

Central evaluation of changes in SI joint inflammation (for the key secondary endpoint) was performed by duplicate independent readings of MRI scans for each subject. The readers were additionally blinded to the chronological order of the scans and the scores of other readers to reduce bias. The dosing instructions will also advise use should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of nr-Axial SpA, which will most likely be rheumatologists to ensure appropriate diagnosis of patients. This is also a disease for which the natural history is not well defined

and patients may spontaneously remit. It is not clear what proportion of patients may relapse following cessation of treatment, or the proportion of patients likely to respond to NSAIDs alone.

The indication restriction to require objective signs of inflammation as indicated by elevated CRP and/or MRI evidence is appropriate given the supportive subgroup analysis results and slightly increased efficacy in the objective signs of inflammation target population, however these comparisons were not adjusted for multiplicity and should therefore be interpreted with caution. Patients with no MRI evidence or elevated CRP did not demonstrate a treatment benefit and will be excluded by the indication. Females had a lower ASAS response than males but still trended in favour of golimumab in the indicated population.

Safety

The safety profile of golimumab in the nr-Axial SpA population appeared comparable with the known safety profile for other rheumatological indications. Although there is up to one year of data, the size of the study population is limited and less than 100 were exposed for a year, which limits the understanding of the safety profile in this new population. However considering the availability of safety data from AS and other rheumatological populations, then this is acceptable. Nevertheless, the potential for serious infections, malignancies, hypersensitivity reactions, injections site reactions and antibody development remains present in this population. Antibody development was reported and all were neutralising antibodies.

RMP

An acceptable RMP has been provided along with acceptable assurances from the sponsor to address outstanding matters.

Overall

The Delegate considers the efficacy and safety of golimumab at the dose requested to be satisfactorily established for the new indication of non-radiographic axial spondyloarthritis pending further advice from ACPM and the PI changes requested herein.

Data deficiencies

The size and duration of exposure to golimumab is limited. There is a lack of data on disease modifying effects, for example structural changes. The pivotal study only included patients aged 18 to 45 years.

Conditions of registration

The following are proposed as conditions of registration and the sponsor is invited to comment on this in the Pre-ACPM response:

1. The implementation in Australia of the EU Risk Management Plan for Simponi (golimumab), version 15.0 (dated 2 February 2016, DLP 6 October 2015), with the Australian Specific Annex, version 4.1 (dated 29 March 2016), included with submission PM-2015-01879-1-3, and the sponsor's response to the RMP dated 28 May 2016 and the responses in the Pre-ACPM Response dated [date], and any subsequent revisions, as agreed with the TGA.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

- What further data/studies are planned or ongoing in nr-Axial- SpA for golimumab? Are any of these studies expected to assess the effects of golimumab on long term disability or radiographic progression (structural change)?

Delegate's considerations

The primary issues with this submission are as follows with further information in the Discussion section:

1. There is some uncertainty whether AS and nr-Axial SpA represent distinct but overlapping disorders or simply different points in the severity or chronology of illness along a single spectrum. Patients may also spontaneously remit.
2. The pivotal study only included patients aged 18 to 45 years.
3. The sponsor has been requested to include a statement regarding suitable treatment duration before continued therapy should be reconsidered in patients not responding.

Delegate's proposed action

The Delegate had no reason to say, at this time, that the application for Simponi should not be approved for registration, pending further advice from ACPM.

The Delegate's suggested wording for the indications is:

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

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does ACPM consider the nr-Axial SpA population to be adequately defined in the clinical studies?
2. Does ACPM consider the age range of the study population acceptable given the nature of the disease?
3. What would be an acceptable period of treatment for a clinical response to be achieved before continued therapy should be reconsidered for non-responders?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Janssen would like to take the opportunity to respond to the issues raised by the Delegate in the request for ACPM advice. The issues raised by the Delegate appear in bold font followed by the sponsor (Janssen's) response.

Delegate's questions for ACPM

1. *Does ACPM consider the nr-Axial SpA population to be adequately defined in the clinical studies?*

Janssen's response

Janssen followed the accepted criteria and have taken appropriate steps to ensure that the AS population is differentiated from the nr-Axial SpA population. The extension of indication for Simponi to include nr-Axial SpA as a distinct disorder/disease entity that warrants biologic treatment is consistent with the current approved Australian PI for entanercept.

In the GO-AHEAD trial (Study P07642), the nr-Axial SpA population was well-defined. Subjects who were eligible and were entered into the clinical study were those who had a physician's diagnosis of active Axial SpA according to established ASAS classification criteria for Axial SpA and had centrally read x-rays that did not fulfil the modified radiographic New York criteria for AS. In addition, subjects must have had an inadequate response to NSAIDs and active disease at screening and baseline with total back pain VAS score ≥ 40mm and BASDAI score of ≥ 40mm on VAS scale of 0-100mm.

2. *Does ACPM consider the age range of the study population acceptable given the nature of the disease?*

Janssen's response

It is believed that nr-Axial SpA is in general an earlier disease in the overall spectrum of Axial SpA; available evidence indicates that the majority of newly diagnosed patients with Axial SpA can be expected to have nr-Axial SpA, and if left untreated nr-Axial SpA can progress to AS. The ASAS classification criteria for Axial SpA includes an age criterion of < 45 years for onset of symptoms[5], and to help ensure the trial captured a true non-radiographic Axial SpA population, the trial included only adult subjects who were ≥ 18 and ≤ 45 years of age.

3. *What would be an acceptable period of treatment for a clinical response to be achieved before continued therapy should be reconsidered for non-responders?*

Janssen's response

Janssen feels an acceptable period of treatment for a clinical response is usually within 12 weeks (after 3 to 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

The Dosage and Administration section of the PI has been amended to reflect this information.

Delegate's questions for the sponsor

1. *What further data/studies are planned or ongoing in nr-Axial SpA for golimumab? Are any of these studies expected to assess the effects of golimumab on long term disability or radiographic progression (structural change)?*

Janssen's response

A post-marketing commitment study is planned for the EU but the study does not address radiographic progression. In AS, anti-TNFs are approved but have not displayed an impact on radiographic progression. The primary objective of the post-marketing commitment study is to evaluate the effect of treatment withdrawal versus continued treatment with golimumab administered SC (either monthly or bi-monthly) on the incidence of disease-

[5] Rudwaleit, ARD. The development of Assessment of SpondyloArthritis. s.l. : International Society Classification criteria for axial spondyloarthritis (part II): validation and final selection, 2009.

activity flare during up to 12 months in adults with active nr-AxSpA who attain inactive disease after receiving open– label golimumab during a 10 month run-in.

Delegate comments on the RMP

The following outstanding matters should be followed up by the sponsor with the RMP evaluator and in the Pre-ACPM Response where required:

a. *Statement on potential for medication errors in the EU SPC. The sponsor should explain why it was included in the EU SPC and whether this was based on reports of medication errors.*

Janssen's response

The Precaution regarding medication errors was added to the EU SmPC as a result of the Pharmacovigilance Risk Assessment Committee (PRAC) assessment report dated 13 June 2013 for the 100 mg Line Extension. The PRAC, having considered the data submitted for the new 100 mg presentation, was of the opinion that the proposed risk minimisation measures were not sufficient to minimise the risks of the product in relation to medication errors. Therefore, the PRAC advised that the market authorisation holder (MAH) should make proposals for the SmPC of the product to accurately reflect and emphasise the restricted use of the 100 mg pen in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. In summary, this statement was added to accurately reflect when 100 mg should be used and not due to actual reports based on medication errors.

Conclusion

Janssen thanks the Delegate for their overview and agrees that the application for Simponi should be approved for registration, for the following indication:

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

Advisory committee considerations

The ACPM resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Simponi solution for injection, prefilled syringe and pen containing 50 mg/0.5 mL and 100 mg/1 mL of golimumab to have an overall positive benefit–risk profile for the indication;

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

In making this recommendation the ACPM

- noted that the subgroup of patients in the clinical study GO-AHEAD with both negative MRI and normal CRP at baseline did not demonstrate a benefit on treatment.
- noted that patients should have persistently elevated C-reactive protein (CRP) and/or consistent MRI evidence to be present for the diagnosis of the non-radiographic axial spondyloarthritis.

- noted that although there may be spontaneous remission in non-radiographic axial spondyloarthritis, the goal is to treat patients early and there is no benefit in delaying treatment.
- advised that the inclusion of 'severe' to describe non-radiographic axial spondyloarthritis in the indication is not required.
- noted that there is no clinical evidence for the use of DMARD therapy in non-radiographic axial spondyloarthritis.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the EU Risk Management Plan

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does ACPM consider the nr-Axial SpA population to be adequately defined in the clinical studies?*

The ACPM agreed that the nr-Axial SpA population is adequately defined in the GO-AHEAD clinical study.

2. *Does ACPM consider the age range of the study population acceptable given the nature of the disease?*

The ACPM agreed that the age range of the study population is acceptable given the epidemiology of the disease.

3. *What would be an acceptable period of treatment for a clinical response to be achieved before continued therapy should be reconsidered for non-responders?*

The ACPM advised that 12 to 16 weeks would be an acceptable period for treatment for a clinical response.

The ACPM advised that 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 containing golimumab (rmc) for the new indication:

Non-radiographic axial spondyloarthritis (nr-Axial SpAJ

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

Specific conditions of registration applying to these goods

1. The Simponi (golimumab) EU Risk Management Plan (RMP), version 15.0, (dated 2 February 2016, OLP 6 October 2015), with the Australian Specific Annex, version 4.1 (dated 29 March 2016), and the sponsor's response to the RMP evaluation report dated 28 May 2016, included with submission PM-2015-01879-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission(s):
    a. Final study report for MK-8259-038.

Attachment 1. Product Information

The PI for Simponi approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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