Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Golimumab (rmc)

Proprietary Product Name: Simponi

Sponsor: Janssen Cilag Pty Ltd

Date of first round report: 01 October 2015
Date of second round report: 14 April 2016

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.
- 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 <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

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

Contents

List of 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
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
placebo	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
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)

1. Introduction

This is a Type C submission to extend the indications for golimumab to include non-radiographic Axial Spondyloarthritis (nr-Axial SpA).

1.1. Drug class and therapeutic indication

According to the Anatomical Therapeutic Chemical (ATC) classification system Simponi (golimumab) is classified as a tumour necrosis factor alpha (TNF-α) inhibitor with ATC subgroup code L04AB06. TNF-α 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, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS).

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 approved indications 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 sponsor proposes to add a new sub-heading of 'Axial Spondyloarthritis' 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).

Comment: 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).

1.2. Dosage forms and strengths

The following dosage forms and strengths of golimumab are currently registered.

Table 1: Strengths and dosage forms of golimumab currently registered

AUST R	Trade Names	Strength	Dosage Form (Pack / container)
153767	Simponi	50 mg	Solution for injection (pre-filled syringe)
153181	Simponi SMARTJECT INJECTOR	50 mg	Solution for injection (pre-filled pen)

AUST R	Trade Names	Strength	Dosage Form (Pack / container)
208278	Simponi	100 mg	Solution for injection (pre-filled syringe)
208279	Simponi SMARTJECT INJECTOR	100 mg	Solution for injection (pre-filled pen)

No new dosage forms or strengths are proposed.

1.3. Dosage and administration

The approved dosage and administration recommendations for golimumab are as follows:

> *Simponi treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or ulcerative colitis.*
>
> *After proper training in SC injection technique, patients may self-inject with Simponi if their physician determines that this is appropriate, with medical follow-up as necessary*.

For the RA, PsA and AS indications, golimumab 50 mg is given as a subcutaneous (SC) injection once a month on the same date each month.

For the UC indication, golimumab 200 mg is given as a SC injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks, thereafter.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

For the proposed non-radiographic axial spondyloarthritis (nr-Axial SpA) indication, golimumab 50 mg is given as a subcutaneous (SC) injection once a month on the same date each month.

1.4. Other proposed changes to the PI

The sponsor proposes changes to the Pharmacology, Clinical Trials, and Precautions sections of the PI. The proposed changes are as follows:

- the addition of PD and PK changes seen in nr-Axial SpA
- the addition of the methodology, subject characteristics, and results of the GO-AHEAD study (Study P07642) in patients with nr-Axial SpA (including immunogenicity).

The details of these recommendations are beyond the scope of this AusPAR.

2. Clinical rationale

In the Clinical Overview, the sponsor has described the submission 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.

3. Contents of the clinical dossier

3.1. Scope 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).

3.2. Paediatric data

The submission did not include paediatric data.

3.3. 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.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

There were no submitted 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 in *Clinical safety, Laboratory tests* below.

4.2. Summary of pharmacokinetics

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

4.2.1. Pharmacokinetics (based on current Australian PI)

Following subcutaneous (SC) administration of Simponi to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics was observed over a dose range of 50 mg to 400 mg. Median terminal half-life values were estimated to be 12 ± 3 days in healthy subjects and similar half-life values were observed in patients with RA, PsA, AS or ulcerative colitis (UC).

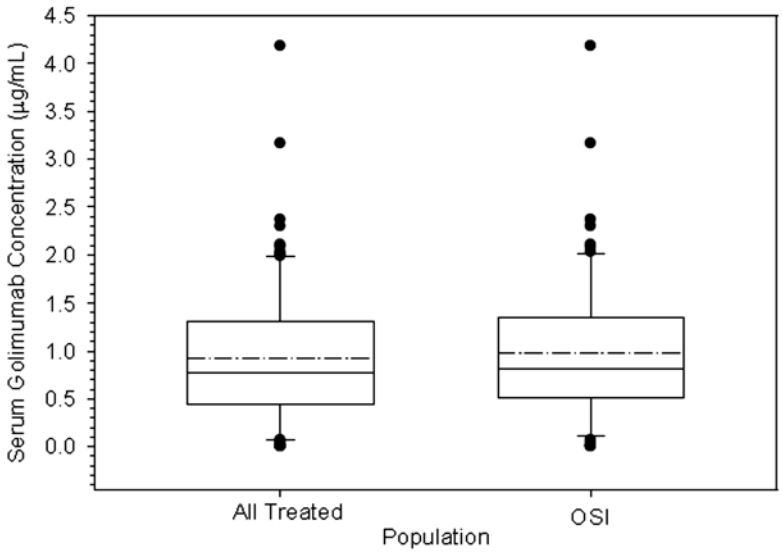
When 50 mg Simponi was administered SC to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by Week 12. With concomitant use of MTX, treatment with 50 mg Simponi SC every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 μg/mL in patients with active PsA and approximately 0.6 μg/mL in patients with AS. Patients with RA, PsA and AS treated with Simponi 50 mg and MTX had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of golimumab, respectively, compared with those treated with Simponi 50 mg without MTX.

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

4.2.2. Pharmacokinetics in the target population

Serum golimumab concentrations at Week 16 in Study P07642 were evaluated in two nr-Axial SpA populations: all subjects treated and the objective signs of inflammation (OSI) subpopulation, which was defined as subjects with baseline evidence of sacroiliitis on MRI and/or screening CRP level > upper limit of normal (ULN). Median golimumab concentrations at Week 16 were the same in both populations (0.8 μg/mL) (Figure 1 1, below). All samples from subjects randomised to placebo showed golimumab concentrations <0.039 μg/mL, the lower limit of quantification for the assay.

Figure 1: Mean (dot-dashed line), Median (solid line), and Interquartile Range for GLM Concentration at Week 16 in Study P07642 for All Treated Subjects and OSI Population



OSI= objective signs of inflammation; Q4W=every 4 weeks; SC=subcutaneous.

When analysed by weight quartiles, a trend for lower concentrations for subjects in the higher weight quartiles was observed; a similar trend was seen using a weight cut off of 100kg although there were few subjects (6/92) who weighed more than 100 kg (Table 2, below).

Table 2: Summary of Steady-state Serum GLM Concentrations (µg/mL) after 50 mg GLM SC at Week 16 by Baseline Weight Quartiles; Subjects Treated with Golimumab in Study P07642

	Golimumab			
	Q1	Q2	Q3	Q4
Study P07642 (nr-Axial SpA)	≤65.4 kg	>65.4 to ≤79.2 kg	>79.2 to ≤86.3 kg	>86.3 kg
50 mg SC golimumab				
N	23	23	23	23
Mean (SD)	1.09 ± 0.984	1.12 ± 0.578	0.91 ± 0.715	0.61 ± 0.433
Median	0.87	1.14	0.73	0.62
IQ range	(0.44, 1.40)	(0.57, 1.39)	(0.37, 1.51)	(0.20, 0.83)
Range	(0.0, 4.2)	(0.2, 2.4)	(0.0, 2.3)	(0.0, 1.55)

4.3. Evaluator's overall 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 ~0.6 µg/mL (according to the current Australian approved Simponi PI) or 0.7 µg/mL (at Week 104 in Study C0524T09 when the same assay was used[1]). The trend for lower serum GLM concentrations in subjects with nr-Axial SpA weighing >100kg was also observed in population pharmacokinetic analyses for the other rheumatological indications.[2] These findings support the proposed dosage and administration guidelines for nr-Axial SpA in the PI.

[1] In the AS study (C0524T09) a different (BioVeris) ECLIA method was used up to Week 52 (data in PI), with the MSD ECLIA used to measure GLM concentrations from Week 104.

[2] Current approved Australian SIMPONI PI dated 6 July 2015

5. Pharmacodynamics

There were no submitted 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.

5.1. Summary of pharmacodynamics

A reduction in CRP is indicative of improvement. There was a significantly greater reduction in CRP at Week 16 in subjects in the GLM 50mg group than in the placebo group (-0.99 mg/dL versus -0.35 mg/dL, respectively; p=0.0003) (Table 3Table, below).

Table 3: Analysis of Change from Baseline in CRP (mg/dL) by Time Point Full-Analysis-Set Population (Part 1, Study P07642)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change From Baseline at Time Point† Mean (SE)	(95% CI)	Difference vs Placebo† Estimate (95% CI)	p-value
Week 4							
GLM 50mg	95	1.51 (2.893)	0.53 (1.848)	-0.91 (0.149)	(-1.21 to -0.62)	-0.70 (-1.05, -0.35)	0.0001
Placebo	99	1.30 (2.009)	1.14 (1.829)	-0.21 (0.146)	(-0.50 to 0.07)		
Week 8							
GLM 50mg	92	1.48 (2.878)	0.57 (1.419)	-0.88 (0.162)	(-1.20 to -0.56)	-0.71 (-1.07, -0.36)	0.0001
Placebo	94	1.19 (1.979)	1.07 (1.728)	-0.16 (0.160)	(-0.48 to 0.15)		
Week 16							
GLM 50mg	88	1.51 (2.937)	0.43 (0.871)	-0.99 (0.181)	(-1.35 to -0.63)	-0.64 (-0.98, -0.30)	0.0003
Placebo	91	1.36 (2.078)	1.06 (1.636)	-0.35 (0.179)	(-0.71 to -0.00)		

† Derived using a constrained longitudinal data analysis (cLDA) model include terms for treatment, week, baseline evidence of sacroiliitis on MRI (yes or no), screening CRP level (<=upper limit of normal/ > upper limit of normal) and treatment by week interaction.

5.2. Evaluator's overall 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.

6. 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. Dose finding studies for the initial registration of golimumab for RA, PsA and AS were evaluated by the TGA previously.

Comment: 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.

7. Clinical efficacy

7.1. Non-radiographic axial spondyloarthritis

7.1.1. Pivotal efficacy study

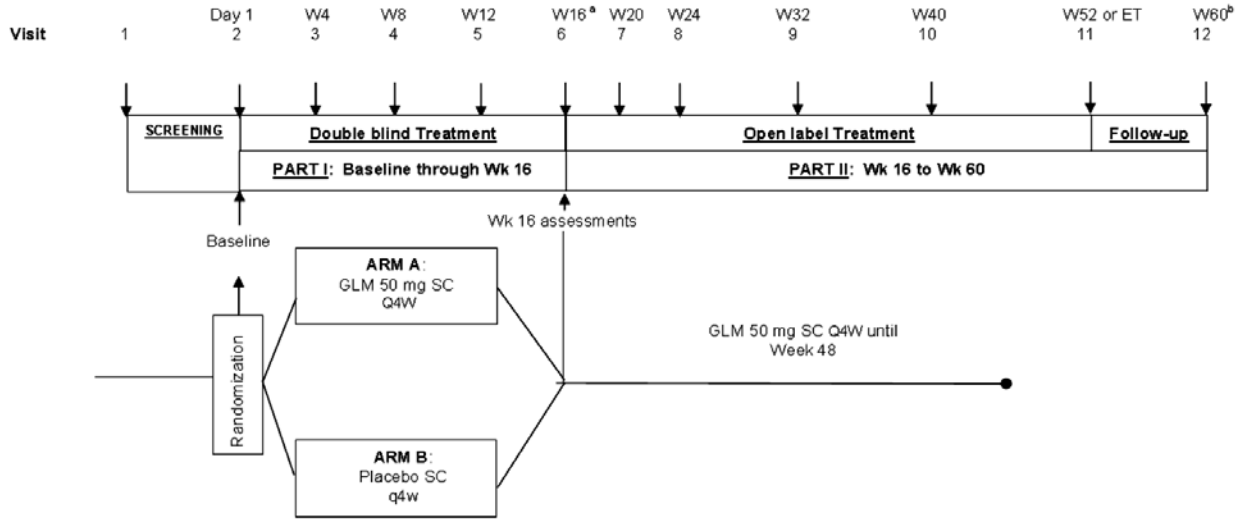
7.1.1.1. Study P07642 (GO-AHEAD)

Study design, objectives, locations and dates

Study P07642 was a Phase IIIb, multicentre, two-part, randomised, double-blind, placebo-controlled study of golimumab administered subcutaneously (SC) in subjects with nr-Axial SpA. The study included a 16-week double-blind, placebo-controlled period (Part 1), followed by a 44-week open-label treatment period (Part 2) which is ongoing. The total duration of the study is 60 weeks. Subjects who successfully completed Part 1 (Weeks 0-16) of the study were eligible to participate in Part 2 (Weeks 16-60). The primary efficacy objective was to evaluate the effect of golimumab (50mg SC at 4-weekly intervals) versus placebo as measured by the primary endpoint, the proportion of subjects who achieve a 20% improvement in response according to the Assessment in Ankylosing Spondylitis International Working Group (ASAS-20) at Week 16. The study schema for P07642 is presented in Figure 2, below. The study was conducted at 66 trial centres: 6 in the Czech Republic, 4 in Denmark, 5 in Finland, 10 in Germany, 3 in Greece, 1 in Ireland, 3 in Italy, 13 in Russia, 3 in Slovakia, 3 in Spain, 6 in Turkey, 4 in the United Kingdom, and 5 in the United States. First patient, first visit occurred on 22 February 2012 and the study is ongoing.

The sponsor has submitted the 24-week clinical study report (CSR) with a cut-off date of 6 May 2014 (when the last subject completed the Week 24 visit). Efficacy is based primarily on the Week 16 data (the placebo-controlled period), with additional data presented to Week 24 to demonstrate maintenance of effect.

Figure 2: Study Flowchart



ET = early termination; GLM = golimumab; SC = subcutaneous; W, Wk = week. a: After Week 16, subjects are allowed to add NSAIDs, methotrexate, sulfasalazine, or hydroxychloroquine. b: Patients who complete the Week 52 visit will have a safety follow-up phone call at Week 60 (12 weeks after the last dose of trial medication). Patients who discontinue the treatment early will have a safety follow-up phone call 12 weeks after the last dose of trial medication.

Comment: The study design and duration of the placebo-controlled period is consistent with that recommended in the EMEA Guideline on Clinical Investigation of Medicinal

Products for the Treatment of Ankylosing Spondylitis for demonstrating improvement in symptoms and disease activity or function.

Inclusion and exclusion criteria

Males and females aged 18 – 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 non-steroidal anti-inflammatory drugs (NSAIDs) were eligible for inclusion. In addition, each subject had to meet either criterion 'a' or 'b' as adopted from the Assessment in Spondyloarthritis International Society (ASAS) classification criteria for the diagnosis of SpA:

a. Active inflammation on MRI highly suggestive of sacroiliitis associated with spondyloarthropathy (as evidenced by the central reader) *and 1 or more* of the following spondyloarthritis characteristics OR

b. HLA-B27+ gene *and 2 or more* of the following spondyloarthritis characteristics (not including HLA-B27):

- Inflammatory back pain, defined as having at least 4 out of the 5 following parameters:
  - age at onset < 40 years;
  - insidious onset;
  - improvement with exercise;
  - no improvement with rest;
  - pain at night (with improvement upon getting up);
- Arthritis diagnosed by a physician;
- Enthesitis (heel) diagnosed by a physician:
  - Spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus;
- Dactylitis diagnosed by a physician;
- Psoriasis diagnosed by a physician;
- History of inflammatory bowel disease (IBD) diagnosed by a physician;
- History of uveitis confirmed by an ophthalmologist;
- Good response to NSAIDs;
  - Note: Good response is defined as '24-48h after a full dose of NSAID the back pain is not present anymore or is much better'.
- Family history for SpA:
  - Presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces and nephews) relatives of any of the following: (1) AS; (2) psoriasis; (3) acute uveitis; (4) reactive arthritis; (5) IBD;
- Elevated CRP (based on central lab values);
- HLA-B27+ gene;

SpA disease activity criteria also had to be met, as well as tuberculosis and laboratory assessment criteria.

Exclusion criteria were extensive. Subjects 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), or had ever received TNF-α targeted therapy, biological agents, cytotoxic drugs, or disease modifying anti-rheumatic drugs (DMARDS) within a specified off-drug period prior to screening.

Comment: Inclusion and exclusion criteria were appropriate and consistent with the ASAS classification criteria for the diagnosis of nr-Axial SpA and were also consistent with the EMEA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Patients with a diagnosis of AS that were based on the modified NY criteria for definite diagnosis of AS were excluded from the study. This was based on central reading of a conventional X-ray performed at Screening. For subjects who had a sacroiliac (SI) joint X-ray performed within 3 months prior to Screening, this X-ray could be sent for central reading. If these X-rays were evaluable by central reading then these patients did not need to have a SI joint X-ray repeated at Screening. It is not known whether some of these patients may have progressed to meet the criteria for AS between the time of X-ray and study entry, and therefore should have been excluded. The sponsor will be asked to provide the number of patients whose inclusion was based on an historical SI joint X-ray, and to report the length of time prior to screening when the X-ray was performed for each of these individuals. However it is considered unlikely that this would be a major concern as in a cohort study of 95 patients with nr-Axial SpA, the rate of progression from nr-Axial SpA to AS over 2 years was 11.6% [1]. Therefore progression over 3 months is likely to occur in a much smaller percentage of patients.

Study treatments

Subjects were administered the following treatments:

Part 1 (Placebo-controlled period):

- Arm A: Subjects received golimumab 50 mg SC injections every 4 weeks (Q4W) at Day 1 (baseline) and at Weeks 4, 8, and 12. NB: use of the abbreviation 'GLM' in this report refers to golimumab 50 mg.
- Arm B: Subjects received placebo SC injections at Day 1 and at Weeks, 4, 8, and 12.

The SC injections in Part 1 were administered in the clinic by site personnel, who also trained subjects on the appropriate method of administration of study drug in preparation for self-administration at home during Part 2 of the study.

Part 2 (Open-label period):

- Arm A and Arm B: All subjects received golimumab 50 mg SC at Week 16 (after completion of all visit assessments) and every 4 weeks thereafter, with the final dose to be administered at Week 48.

All subjects were allowed to remain on a stable daily dose of NSAIDS during the study as long as this dosage was initiated at least 30 days prior to Screening. New NSAIDs could be initiated after Week 16 at the investigator's discretion.

Comment: Placebo controlled, parallel group studies are recommended the EMEA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. Maintenance of a stable dose of NSAIDs (where effective), is also consistent with this Guideline.

Efficacy variables and outcomes

The main efficacy variables are listed below.

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Patient's Global Disease Assessment
- Total Back Pain
- Nocturnal Back Pain
- MRI of the SI joints
- EuroQoL-5D Health Questionnaire (EQ-5D)
- Work Productivity and Activity Impairment (WPAI)
- Short Form-36
- Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)
- CRP

Musculoskeletal Assessments:

- Swollen and Tender Joint Count
- Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Maastricht Ankylosing Spondylitis Enthesitis Score Index (MASES)
- Measure Chest Wall Expansion
- Physician's Global Assessment

The primary efficacy outcome was the effect of golimumab versus placebo as measured by the primary endpoint, the proportion of subjects who achieve an ASAS-20 response at Week 16. ASAS domains are measured on a scale of 0 to 100 mm (with 0 being the very best and 100 being the very worst situation). An ASAS-20 response is defined as meeting both the following criteria:

1. An improvement of ≥ 20% from Baseline and an absolute improvement from Baseline of ≥10 mm in at least 3 of the following 4 domains:
    a. Patient global assessment
    b. Pain (total back pain)
    c. Function (BASFI)
    d. Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness)
2. Absence of deterioration from Baseline (≥20% and an absolute change of ≥10 mm) in the potential remaining domain.

The key secondary efficacy outcomes were:

- the proportion of subjects who achieve ASAS-40 response at Week 16.
- the proportion of subjects who achieve BASDAI 50 response at Week 16.
- the proportion of subjects who achieve ASAS partial remission at Week 16.
- the change in the SPARCC MRI SI joints scoring from Baseline to Week 16.

Other secondary efficacy outcomes included:

- Change in Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Change in C-reactive protein (CRP)

- Proportion of subjects achieving ASAS 5/6
- Change in Ankylosing Spondylitis Disease Activity Score CRP (ASDAS-C)
- Proportion of subjects achieving low ASDAS-C (<1.3)
- Proportion of subjects achieving ASAS-20
- Proportion of subjects achieving ASAS-40
- Proportion of subjects achieving 50% reduction in BASDAI
- Proportion of subjects in ASAS partial remission
- Change in swollen and tender joint count
- Change in chest wall expansion
- Change in Patient Reported Outcomes (PROs)
  - 36-item Short Form Health Survey (SF-36)
  - Ankylosing Spondylitis Quality of Life (ASQoL)
  - EuroQoL 5D Health Questionnaire (EQ-5D),
  - Work Productivity and Activity Impairment (WPAI),
  - Patient's Global Disease Assessment Visual Analog Scale (VAS),
  - Total Back Pain VAS,
  - Nocturnal Pain VAS
- Change in Physician's Global VAS
- Change in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index

Comment: The individual efficacy variables measured several aspects of disease activity by means of validated scales and instruments as recommended by the EMEA Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis.

The ASAS-20 is a validated composite endpoint of validated individual assessment scales and is considered an appropriate primary efficacy endpoint for NSAIDs and other (non-specified) products by the Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. The Guideline suggests that the ASAS-40 'may be required in certain circumstances', and states that because 'the ASAS composite does not include the assessment of the spine mobility, which is a relevant efficacy parameter in AS', 'Spinal mobility must be considered either a co-primary endpoint or an important secondary endpoint'. While it is not clear whether this should also be required for nr-Axial SpA, Study P07642 measured the ASAS-40 as a key secondary endpoint and included spinal mobility [BASMI and chest expansion], and other secondary endpoints consistent with the Guideline.

Randomisation and blinding methods

In Part 1 of the study, subjects were randomised to treatment in a 1:1 ratio via an Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS). Randomisation was stratified by:

3. Evidence of sacroiliitis (active inflammation) on MRI. Subjects without evidence of sacroiliitis were limited to 50% of the total enrolled subject population.
4. CRP level (≤ULN/ > ULN). Subjects with normal CRP level at screening (according to the central lab) were limited to 60% of total enrolled subject population.

The percentage of subjects without evidence of sacroiliitis (30% in the original protocol) and with normal CRP level at screening (not specified in the original protocol) were modified as a protocol amendment (1 Feb 2013) to ensure that subjects had active inflammation at study entry. The sponsor stated that this '*would continue to allow for the detection of meaningful clinical and radiographic treatment effects in subjects treated with an anti-TNF agent*.'

Part 2 of the study was not randomised.

The investigator, study nurse, study participant, and sponsor personnel were blinded to the treatment group assignments in Part 1 of the study. Blinding was maintained using an IVRS/IWRS. Data that could potentially unblind the treatment assignment (that is,, CRP values and MRI scores) were masked prior to unblinding. Part 2 of the study was open-label.

X-rays and MRIs were read centrally by readers blinded to treatment assignment, clinical information, and results of investigator readings. Central confirmation of subject X-ray eligibility and MRI stratification was based on a single reading of Screening Visit X-rays and MRI scans of the SI joints, respectively. 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. Discordant results between the two readers were adjudicated by a third reader.

Comment: The protocol amendment to ensure that subjects had active inflammation at study entry is not considered to have adversely affected the power of the study to detect a treatment difference between GLM and placebo on the primary efficacy outcome (see also Section *Pivotal efficacy study*, below).

Analysis populations

Efficacy data for Part 1 and Part 2 were analysed separately. The primary analysis of all efficacy variables was performed using the Full Analysis Set (FAS) also referred to as the All Subjects as Treated set (ASaT), which consisted of all randomised subjects who received at least one dose of study treatment in either Part 1 or Part 2 of the study (Table 4, below).

A supportive, Per-Protocol (PP) analysis was conducted for the primary efficacy endpoint. The PP population excluded subjects based on a set of pre-specified criteria (e.g., violations on the exclusion and inclusion criteria, low medication compliance/adherence, or use of prohibited medications during Part 1) that according to the sponsor '*may substantially affect or confound the measures of efficacy or the intended claims for the compound*.'

Subjects were included in the treatment group to which they were randomised for the analysis of efficacy data using both the FAS and PP populations.

An additional efficacy population was added prior to study unblinding. The Objective Signs of Inflammation (OSI) Population consisted of subjects with baseline evidence of sacroiliitis on MRI and/or screening CRP level >ULN. This subgroup was added by the sponsor '*based on the EMA Assessment report for Humira which became available after the Go Ahead protocol was finalized. The EMA Assessment report published as a European Public Assessment Report (EPAR) in September 2012 stated that 'the CHMP required a change to the indication wording requiring the presence of an elevated CRP and/or a positive MRI in the target population'. The viewpoint of the CHMP was reiterated in the EPAR summarizing a similar variation for Cimzia, which was published in November, 2013*.'

Table 4: Efficacy Analysis Populations

Analysis Set Name	Type	Multiplicity Adjustments	Study Phase	Placebo N	Golimumab 50 mg N	Total N	Definition
Full Analysis Set (FAS)	Pre-specified	yes	Part 1	100	97	197	All randomized subjects who received at least 1 dose of study treatment during Part 1.
		no	Part 2	96	93	189	All randomized subjects who received at least 1 dose of study treatment during Part 2.
Per Protocol (PP)	Pre-specified	no	Part 1	87	87	174	All FAS subjects excluding subjects based on a set of pre-specified criteria.
Objective Signs of Inflammation (OSI) Population	Pre-specified	no	Part 1	80	78	158	The subset of FAS subjects who had elevated CRP and/ or MRI evidence of sacroiliitis at randomization.

Comment: While technically a post-hoc analysis, given the basis and timing of the decision to add the OSI population analysis (prior to unblinding), this is considered appropriate.

Subgroup analyses were performed for the following variables:

- Demography
- Gender (Male, Female)
- Race (Caucasian, Black, Asian, Other)
- Age (≤30, >30 years)
- Weight (below or at median, above median)
- Baseline laboratory results
- HLA-B27 (positive, negative).
- Baseline disease characteristics
- Baseline MRI sacroiliitis (Yes, No),
- Baseline disease duration (below or at median, above median),
- Baseline BASDAI score – (below or at median, above median),
- Baseline CRP (≤ULN/ > ULN).
- Baseline medications
- Use of NSAIDs (yes, no)
- Geographic location
- Region (region will be defined based on the participant countries and appropriate groupings will be done if the number of subjects for a geographic region is small)

Sample size

The target sample size for the study was 200 subjects. For the primary hypothesis, with 100 subjects per group, there was at least 95% power to detect a 26% treatment difference between GLM 50 mg and placebo (2-sided, overall α=0.050), assuming the true response rate for placebo group was 25%.

Comment: The placebo response rate was estimated based on two anti-TNF trials in AS [References 2, 3]. This is appropriate.

Statistical methods

The primary and binary response type secondary efficacy endpoints in Part 1 of the study were analysed using the stratified Miettinen and Nurminen method, stratified by baseline evidence of sacroiliitis on MRI (yes or no) and baseline CRP level (≤ULN / >ULN). Other variables were analysed using a constrained longitudinal data analysis (cLDA) model (normally distributed continuous secondary variables), or a Mann-Whitney or Wilcoxon rank sum test (non-normally distributed continuous secondary variables). Subgroup analyses of the primary endpoint were conducted in various pre-specified demographic and baseline factors to assess the consistency of the treatment effect. No multiplicity control was applied to the subgroup analyses.

If the primary efficacy analysis was statistically significant at two-sided α = 0.05, multiplicity adjustment was performed on the four key secondary efficacy endpoints in the order pre-specified below:

- Proportion of subjects achieving ASAS-40 response at Week 16;
- Proportion of subjects achieving at least BASDAI 50 at Week 16;
- Proportion of subjects in ASAS partial remission at Week 16;
- Change in MRI SI joints scoring from Baseline to Week 16.

A closed ordered testing procedure was applied to the four above listed key secondary comparisons to control the overall α level of 0.05. Analyses of the other secondary endpoints were intended to be supportive of the primary and key secondary analyses. No multiplicity adjustment was made. Any p-values presented for these variables are of a descriptive nature only.

In a pre-planned change to the statistical analysis plan made prior to unblinding, a secondary analysis of Week 16 SPARCC MRI SI Joints score change from baseline was performed based on aligned rank test and an analysis of covariance (ANCOVA) with baseline MRI score as a covariate and treatment in the model.

In Part 2 of the study, descriptive statistics of the efficacy endpoints (counts and percentages for binary response type variables; mean, standard error (SE), median and range for continuous variables) will be tabulated and/or plotted by treatment group at each visit.

Missing data imputation strategy

The imputation strategy varied for each of the endpoints.

Participant flow

In total, 393 subjects were screened for study inclusion, 198 subjects were randomised, and 197 received treatment (97 on GLM, 100 on placebo). Of the 195 subjects excluded during screening, 173 (88.7%) were screen failures, and 12 (6.2%) could not be randomised because the stratification cap had already been met.

Study P07642 is currently ongoing. This submission includes interim data collected to a cut-off date of 6 May 2014. At this time, 187 subjects (94.4%) had completed 24 weeks of treatment; 155 subjects (78.3%) had completed 52 weeks of treatment in the open-label period of the

study (Part 2), 24 (12.1%) had discontinued the study, and 21 (10.6%) subjects were ongoing in Part 2. Discontinuation from the trial occurred for 13 (13.3%) subjects from the GLM group and 11 (11.0%) from the placebo group. The most common reasons for discontinuation were: loss to follow-up (4.1% versus 0.0% for GLM & placebo, respectively), adverse event (3.1% versus 3.0%), and subject withdrew consent (2.0% versus 3.0%) (Tables 5 and 6 below).

Table 5: Disposition of randomised subjects (data cut-off 6 May 2014)

	GLM 50mg/GLM 50 mg		Placebo/GLM 50 mg		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	98		100		198	
Trial Disposition						
Completed	62	(63.3)	68	(68.0)	130	(65.7)
Discontinued	13	(13.3)	11	(11.0)	24	(12.1)
Adverse Event	3	(3.1)	3	(3.0)	6	(3.0)
Lost To Follow-Up	4	(4.1)	0	(0.0)	4	(2.0)
Non-Compliance With Protocol	1	(1.0)	2	(2.0)	3	(1.5)
Physician Decision	1	(1.0)	1	(1.0)	2	(1.0)
Pregnancy	1	(1.0)	0	(0.0)	1	(0.5)
Pregnancy Wish	0	(0.0)	2	(2.0)	2	(1.0)
Protocol Violation	1	(1.0)	0	(0.0)	1	(0.5)
Subject Withdrew Consent	2	(2.0)	3	(3.0)	5	(2.5)
Unknown	23	(23.5)	21	(21.0)	44	(22.2)

Unknown: A disposition record did not exist at the time of reporting.

Table 6: Subject status of randomised subjects (data cut-off 6 May 2014)

	Placebo n (%)	Golimumab 50 mg n (%)
Randomized subjects	100	98
Treated subjects[a]	100 (100)	97 (98.9)
Completed Week 16 (Part 1)	97 (97.0)	93 (94.9)
Completed Week 24	94 (94.0)	93 (94.9)
Completed Week 52	78 (78.0)	77 (78.6)
Ongoing as of 06 May 2014	11 (11.0)	10 (10.2)

[a]: Received at least 1 dose of study agent.

Major protocol violations/deviations

Twenty three subjects (13 on GLM, 10 on placebo) were excluded from the PP analysis on the basis of pre-specified criteria: 8 (4%) subjects had violations on the exclusion and inclusion criteria, 9 (4.5%) subjects had low medication compliance or early discontinuation from Part 1 (that is, did not receive all 4 doses of study medication), 4 (2%) subjects used prohibited medications or had unstable NSAID use during Part 1, and 3 (2%) had large visit windows between visits. One subject met two criteria.

One subject did not meet inclusion criterion 3 for nr-Axial SpA diagnosis because they did not have sacroiliitis on MRI and were HLA-B27 negative. As this was not discovered until after the data base lock, this subject was still included in the per-protocol analysis.

Eight sites reported having visual analogue scales that were not the standard 100 mm length. A full investigation was conducted and corrected scales provided. A mathematical formula was used to convert the values recorded on the incorrect scales to the standard scale length.

Baseline data

The 2 treatment groups had similar baseline demographics with the exception of gender. The majority of subjects were male (57.1%) with more males in the GLM than the placebo group (62.2% versus 52%, respectively). The median age was 30.0 years (range: 18 to 46 years), and 100% were 'white'. Disease characteristics were also comparable in the 2 groups, with 67% having a disease duration <1 year, 82% HLA-B27 positive, and more than 50% had failed ≥ 2

prior NSAIDs (Table 7, below). A normal CRP was recorded in 59% of both groups, and evidence of sacroiliitis on MRI was seen in 66-67% of all subjects, as per the protocol stratification rules. Disease activity was also similar, with a mean BASDAI score of 6.6 cm and 6.4 cm, and a mean ASDAS-C score of 3.6 and 3.5 for the GLM and placebo groups, respectively. The majority of subjects in both treatment groups were on an anti-inflammatory/anti-rheumatic product (87.6% versus 83.0%), with the most common products being etoricoxib (21.6% versus 15.0%), diclofenac / diclofenac sodium (23.7% versus 27.0%), nimesulide (14.4% versus 9.0%), ibuprofen (13.4% versus 16.0%), and meloxicam (12.4% versus 14.0%). Drugs for acid-related disorders (20.6% versus 27.0%) and analgesics were also commonly used (18.6% versus 13.0%).

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 (MRI score and CRP levels) (Table 8, below). For example, the mean baseline SPARCC SI MRI score (11.3 versus 14.1) and the mean baseline CRP score (1.40 mg/dL versus 1.68 mg/dL) in the FAS and OSI populations, respectively, were both higher in the OSI population.

Table 7: Selected baseline demographic and disease characteristics (FAS, Part 1)

	GLM 50 mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	98		100		198	
Gender						
Male	61	(62.2)	52	(52.0)	113	(57.1)
Female	37	(37.8)	48	(48.0)	85	(42.9)
Age (Years)						
Less than or Equal to 30	57	(58.2)	45	(45.0)	102	(51.5)
Greater than 30	41	(41.8)	55	(55.0)	96	(48.5)
Mean	30.7		31.7		31.2	
SD	7.1		7.2		7.2	
Median	29.0		32.0		30.0	
Range	18 to 46		18 to 45		18 to 46	
Race						
White	98	(100.0)	100	(100.0)	198	(100.0)
Ethnicity						
Hispanic Or Latino	0	(0.0)	2	(2.0)	2	(1.0)
Not Hispanic Or Latino	96	(98.0)	94	(94.0)	190	(96.0)
Not Reported	0	(0.0)	2	(2.0)	2	(1.0)
Unknown	2	(2.0)	2	(2.0)	4	(2.0)
Screening C-Reactive Protein (CRP)						
<= Upper Limit of Normal	58	(59.2)	59	(59.0)	117	(59.1)
> Upper Limit of Normal	40	(40.8)	41	(41.0)	81	(40.9)
Magnetic Resonance Image (MRI) Sacroiliitis						
Evidence	66	(67.3)	66	(66.0)	132	(66.7)
No Evidence	32	(32.7)	34	(34.0)	66	(33.3)
Human Leukocyte Antigen B27 (HLA-B27)						
Positive	81	(82.7)	82	(82.0)	163	(82.3)
Negative	17	(17.3)	18	(18.0)	35	(17.7)
Stratum						
Evidence of Sacroiliitis on MRI and CRP Level <= Upper Limit of Normal	39	(39.8)	39	(39.0)	78	(39.4)
Evidence of Sacroiliitis on MRI and CRP Level > Upper Limit of Normal	27	(27.6)	27	(27.0)	54	(27.3)
No Evidence of Sacroiliitis on MRI and CRP Level <= Upper Limit of Normal	19	(19.4)	20	(20.0)	39	(19.7)
No Evidence of Sacroiliitis on MRI and CRP Level > Upper Limit of Normal	13	(13.3)	14	(14.0)	27	(13.6)
CRP (mg/dL)						
Subjects with data	97		100		197	
Mean	1.52		1.29		1.40	
SD	2.868		2.002		2.463	
Median	0.48		0.51		0.50	
Range	0.2 to 21.3		0.2 to 11.5		0.2 to 21.3	
SPARCC SI MRI Score						
Subjects with data	91		96		187	
Mean	9.9		12.7		11.3	
SD	12.3		15.4		14.0	
Median	4.0		7.0		5.0	
Range	0.0 to 54.0		0.0 to 63.0		0.0 to 63.0	

Table 8: Selected baseline demographic and disease characteristics (OSI, Part 1)

	GLM 50mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	78		80		158	
Gender						
Male	54	(69.2)	44	(55.0)	98	(62.0)
Female	24	(30.8)	36	(45.0)	60	(38.0)
Age (Years)						
Less than or Equal to 30	48	(61.5)	38	(47.5)	86	(54.4)
Greater than 30	30	(38.5)	42	(52.5)	72	(45.6)
Mean	30.2		31.2		30.7	
SD	6.7		6.9		6.8	
Median	29.0		31.0		30.0	
Range	18 to 46		18 to 45		18 to 46	
Race						
White	78	(100.0)	80	(100.0)	158	(100.0)
Ethnicity						
Hispanic Or Latino	0	(0.0)	2	(2.5)	2	(1.3)
Not Hispanic Or Latino	76	(97.4)	76	(95.0)	152	(96.2)
Not Reported	0	(0.0)	2	(2.5)	2	(1.3)
Unknown	2	(2.6)	0	(0.0)	2	(1.3)
Screening C-Reactive Protein (CRP)						
<= Upper Limit of Normal	39	(50.0)	39	(48.8)	78	(49.4)
> Upper Limit of Normal	39	(50.0)	41	(51.3)	80	(50.6)
Magnetic Resonance Image (MRI) Sacroiliitis						
Evidence	65	(83.3)	66	(82.5)	131	(82.9)
No Evidence	13	(16.7)	14	(17.5)	27	(17.1)
Human Leukocyte Antigen-B27 (HLA-B27)						
Positive	63	(80.8)	62	(77.5)	125	(79.1)
Negative	15	(19.2)	18	(22.5)	33	(20.9)
Stratum						
Evidence of Sacroiliitis on MRI and CRP Level <= Upper Limit of Normal	39	(50.0)	39	(48.8)	78	(49.4)
Evidence of Sacroiliitis on MRI and CRP Level > Upper Limit of Normal	26	(33.3)	27	(33.8)	53	(33.5)
No Evidence of Sacroiliitis on MRI and CRP Level > Upper Limit of Normal	13	(16.7)	14	(17.5)	27	(17.1)
CRP (mg/dL)						
Subjects with data	78		80		158	
Mean	1.83		1.52		1.68	
SD	3.122		2.174		2.680	
Median	0.73		0.67		0.72	
Range	0.2 to 21.3		0.2 to 11.5		0.2 to 21.3	
SPARCC SI MRI Score						
Subjects with data	73		76		149	
Mean	12.3		15.8		14.1	
SD	12.7		15.8		14.4	
Median	8.5		11.0		10.0	
Range	0.0 to 54.0		0.0 to 63.0		0.0 to 63.0	

Comment: Baseline characteristics were generally balanced across the 2 treatment groups, with the exception of gender. The vast majority were HLA B27 positive with a

preponderance of males. Disease duration < 1 year in approximately two-thirds of the subjects is consistent with the possibility that nr-Axial SpA is a precursor to the development of AS, but does not rule out that it is a distinct but 'overlapping disorder.[3] There is potential for the higher proportion of females in the placebo arm to affect the interpretation of the study results, as females showed a smaller treatment difference between GLM and placebo than was expected. However it appears that this is at least partially related to a higher proportion of females having a normal CRP. This should be addressed by specifying patients have objective signs of inflammation (elevated CRP and/or positive MRI evidence) in the indication. The sponsor will be asked for sub-group analyses in the OSI population.

Results for the primary efficacy outcome

The ASAS-20 response rate at Week 16 was significantly higher in the GLM group (71.1%) than in the placebo group (40.0%), a difference of 31.2% (p<0.0001). The supportive PP analysis also resulted in a statistically significant outcome in favour of GLM (Table 9, below).

Table 9: Primary Endpoint: Analysis of the Proportion of Subjects Achieving ASAS-20 Response at Week 16 (Part 1)

Analysis		Responder		Difference in % vs Placebo	
Analysis Set	Treatment	n/N	%	Estimate (95% CI)‡	P-value‡
Primary Analysis	GLM 50 mg	69 /97	71.1	31.2 (17.5, 43.6)	<0.0001
FAS	Placebo	40 /100	40.0		
Sensitivity Analysis	GLM 50 mg	63 /84	75.0	36.4 (22.0, 49.2)	<0.0001
PP	Placebo	35 /90	38.9		

‡ 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.

While no subjects met the treatment failure criteria prior to Week 16, 7 subjects were considered to be non-responders because they discontinued prior to Week 16: 4 (2%) in the GLM group and 3 (1.5%) in the placebo group.

OSI (target) population

In the OSI population, the ASAS-20 response rate at Week 16 was also significantly higher in the GLM group (60/78, 76.9%) than in the placebo group (30/80, 37.5%), a difference of 39.6% (95% CI: 24.6, 52.6; p<0.0001) (Table 10, below).

[3]Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum. 2008 Jul;58(7):1981-91.

Table 10: ASAS-20, ASAS-40, BASDAI 50 and ASAS Partial Remission at Week 16 (OSI, Part 1)

Endpoints	Treatment	Responder		Difference in % vs Placebo	
		n/N	%	Estimate (95% CI)‡	P-value‡
ASAS 20	GLM 50 mg Placebo	60 /78 30/80	76.9 37.5	39.6 (24.6, 52.6)	<0.0001
ASAS 40	GLM 50 mg Placebo	47 /78 18 /80	60.3 22.5	37.9 (23.0, 51.2)	<0.0001
BASDAI 50	GLM 50 mg Placebo	46 /78 23 /80	59.0 28.8	30.5 (15.4, 44.3)	<0.0001
ASAS Partial Remission	GLM 50 mg Placebo	27 /78 15 /80	34.6 18.8	16.1 (2.5, 29.6)	0.0204

‡ 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.

Results for the key secondary efficacy outcomes

Results for the key secondary efficacy outcomes are reported in Tables 11 and 12 below. The response rates at Week 16 were significantly higher in the GLM group than in the placebo group 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. Subjects on GLM showed a significantly greater reduction from baseline in the SPARCC MRI SI joints score than subjects on placebo (-5.3 versus -0.9, respectively; p<0.0001). In the pre-planned secondary approaches to analysing the change in SPARCC MRI SI joints score, both the aligned rank and ANCOVA analyses were consistent with the primary analysis, demonstrating a significantly greater reduction from baseline in the GLM group than in the placebo group (p=0.0005 and p<0.0001 for the aligned rank test and ANCOVA, respectively).

Table 11: Key Secondary Endpoints of ASAS 40, BASDAI 50 and ASAS Partial Remission at Week 16 (FAS, Part 1)

Endpoint	Treatment	Responder		Difference in % vs Placebo	
		n/N	%	Estimate (95% CI)‡	P-value‡
ASAS 40	GLM 50 mg Placebo	55 /97 23 /100	56.7 23.0	33.8 (20.4, 46.1)	<0.0001
BASDAI 50	GLM 50 mg Placebo	56 /97 30 /100	57.7 30.0	28.0 (14.4, 40.6)	<0.0001
ASAS Partial Remission	GLM 50 mg Placebo	32 /97 18 /100	33.0 18.0	15.2 (3.2, 27.1)	0.0136

‡ 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.

Table 12: Key Secondary Endpoint of Analysis of Change from Baseline in SPARCC MRI SI Joints Score at Week 16 (FAS, Part 1)

Treatment	N	Baseline		Week 16 Mean (SD)	Change from Baseline at Week 16 Mean (SD)	Difference vs Placebo †	
		Mean	Median			Score	p-value
GLM 50mg	74	9.9	4.0	4.6 (7.92)	-5.3 (7.71)	-4.3	<0.0001
Placebo	87	12.7	7.0	11.7 (14.79)	-0.9 (8.53)		

† Derived based on Mann-Whitney Test.
Includes subjects with MRI SI joint measurements at Baseline and Week 16

OSI (target) population

In the OSI population, the response rates at Week 16 were also significantly higher in the GLM group than in the placebo group for the ASAS-40 (60.3 versus 22.5%), BASDAI 50 (59.0 versus 28.8%), and ASAS Partial Remission (34.6 versus 18.8%) endpoints (Table 10Table 10, above). Subjects on GLM showed a significantly greater reduction from baseline in the SPARCC MRI SI joints score than subjects on placebo (-6.4 versus -1.2, respectively; p<0.0001). In the pre-planned secondary approaches to analysing the change in SPARCC MRI SI joints score, both the aligned rank and ANCOVA analyses were consistent with the primary analysis, demonstrating a significantly greater reduction from baseline in the GLM group than in the placebo group (p=0.0002 and p<0.0001 for the aligned rank test and ANCOVA, respectively) (Table 13, below).

Table 13: Key Secondary Endpoint of Analysis of Change from Baseline in SPARCC MRI SI Joints Score at Week 16 (OSI, Part 1)

Treatment	N	Baseline		Week 16 Mean (SD)	Change from Baseline at Week 16 Mean (SD)	Difference vs Placebo †	
		Mean	Median			Score	p-value
GLM 50mg	61	12.0	9.0	5.6 (8.41)	-6.4 (8.07)	-3.9	<0.0001
Placebo	69	15.8	10.5	14.6 (15.36)	-1.2 (9.58)		

† Derived based on Mann-Whitney Test.
Includes subjects with MRI SI joint measurements at Baseline and Week 16

Results for other efficacy outcomes

There were numerous other secondary endpoints analysed for supportive purposes. For all endpoints, results were numerically better (showed more improvement) for subjects on GLM than those subjects on placebo.

Subgroup analyses

Subgroup analyses of the primary endpoint were conducted in various pre-specified demographic and baseline factors to assess the consistency of the treatment effect (Figure 3, below). These comparisons were not adjusted for multiplicity and should therefore be interpreted with caution. In the majority of subgroups, the ASAS-20 responses were better in the GLM group compared with the placebo group. The exception was the subgroup who had both a negative MRI and normal CRP at baseline, where there was no difference detected between the treatments (Table 14, below). ASAS-40 responses favoured the GLM group compared with the placebo group in all subgroups.

Because female response rates showed a smaller treatment difference than was expected, this was explored further. It appeared that this 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), and a smaller treatment difference in this stratum compared with the CRP above normal limits stratum (13% versus 28%, respectively in female subjects). The proportion of females and males in the MRI positive stratum was similar (54 [64%] versus 78 [69%], respectively).

Figure 3: Difference in Percent ASAS 20 Responder Status at Week 16 by Baseline Factors Point Estimate and 95% CI GLM 50mg versus placebo (FAS, Part 1)

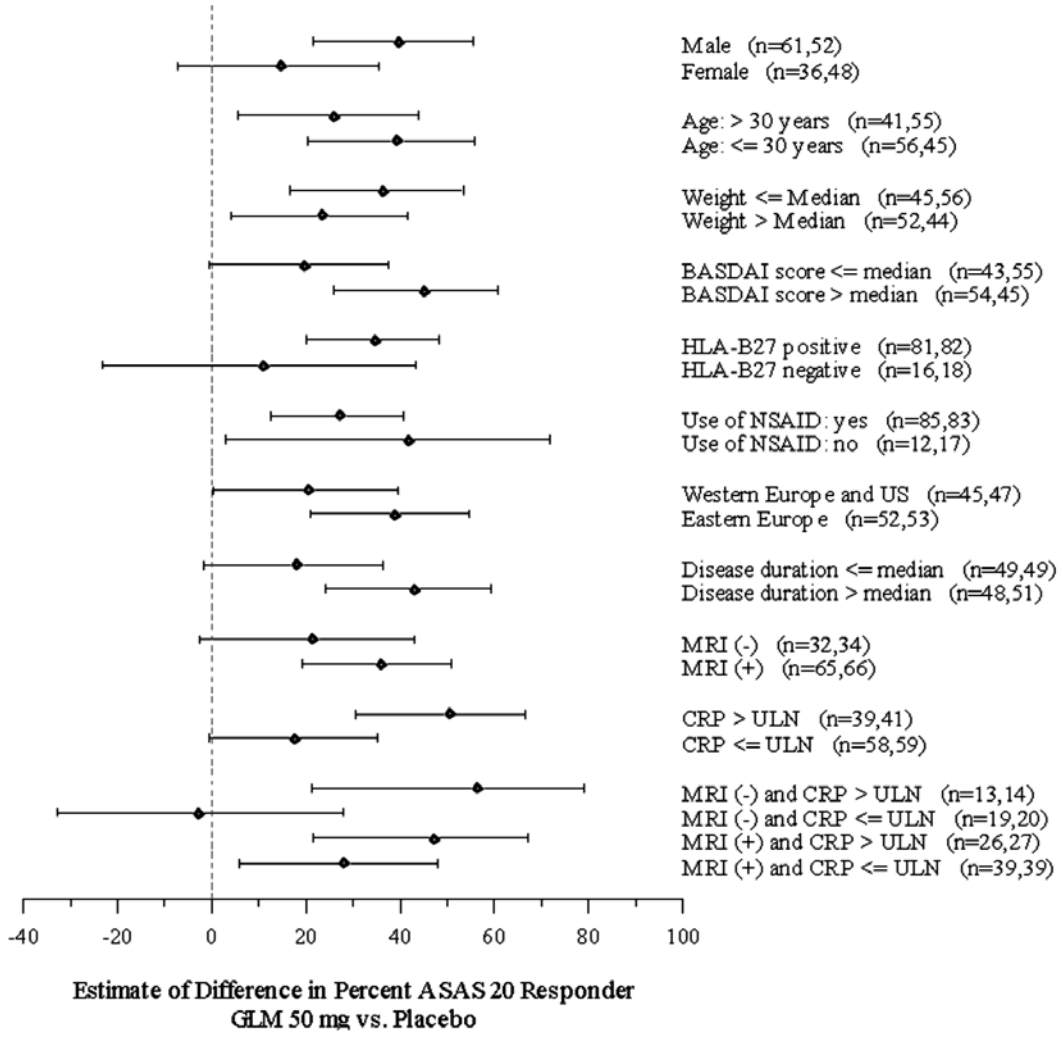


Table 14: Subgroup Analysis of Subjects Achieving ASAS 20 Response at Week 16 by Baseline MRI and Screening CRP (FAS, Part 1)

Treatment	Responder n/N	Responder %	Difference in % vs Placebo Estimate (95% CI)[‡]	Difference in % vs Placebo P-value[‡]
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.

Comment: The proposal to only include patients with an elevated CRP and/or MRI evidence of inflammation in the indication should address the apparent reduced efficacy in women, as it appears that this may be at least partially due to the higher proportion of females with a CRP within the normal limits. To investigate this interpretation, the sponsor will be asked to provide the equivalent of Figure 11-4 from the CSR for the OSI population.

Efficacy and antibodies to golimumab

At Week 16, 4 subjects (4.3%) tested positive for antibodies to golimumab (see also Section Adverse events below). All 4 subjects achieved ASAS-20 (Table 15, below).

Table 15: Subjects Achieving ASAS-20 at Week 16 by Antibody to GLM Status (FAS, Part 1)

	Treatment	
	Placebo N=100	GLM 50 mg N=97
Subjects with appropriate samples [a]	97	93
Subjects positive for antibody to GLM status [b,c]	0 (0.0)	4 (4.3)
Achieved ASAS20	0 (0.0)	4 (100.0)
Subjects negative for antibody to GLM status [b,d]	97 (100.0)	89 (95.7)
Achieved ASAS20	39 (40.2)	65 (73.0)

[a] Subjects with appropriate samples had 1 or more samples obtained after their first study agent administration.
[b] Denominator is subjects with appropriate samples.
[c] Includes all subjects who had at least 1 positive sample at any time.
[d] Includes all subjects whose last sample was negative and excludes subjects who were positive at any time.

Comment: Antibody incidence in subjects with nr-Axial SpA is comparable to that observed across the golimumab Phase 3 RA, PsA and AS studies through week 24 (4.3%). There was no apparent impact of antibody positivity on the effectiveness of treatment with GLM on the basis of the ASAS-20 response.

Efficacy at Week 24 (Part 2)

At week 24 (after 8 weeks open-label therapy with GLM) an ASAS-20 response was observed in 83.9% of patients in the GLM/GLM group and 70.8% in the placebo/GLM group. Response rates were higher in those subjects who were responders at Week 16 than in non-responders, with the vast majority (>90%) of responders at Week 16 having sustained the response (Table 16, below). Similarly for the key secondary endpoints, the response rates were higher for subjects in the GLM/GLM group than the placebo/GLM group, and higher in those subjects who were responders at Week 16 than in non-responders. Results in the OSI population were similar to those observed in the FAS population.

Table 16: Proportion of Subjects Achieving ASAS-20, ASAS-40, BASDAI 50 and ASAS Partial Remission at Week 24 by Week 16 Responder Status (FAS, Part 2)

	Week 16 Responder Status n/N (%)		Total n/N (%)
ASAS 20	Responder	Non-responder	
GLM 50 mg/GLM 50 mg	66/69 (95.7)	12/24 (50.0)	78/93 (83.9)
Placebo/GLM 50 mg	38/40 (95.0)	30/56 (53.6)	68/96 (70.8)
ASAS 40			
GLM 50 mg/GLM 50 mg	51/55 (92.7)	17/38 (44.7)	68/93 (73.1)
Placebo/GLM 50 mg	20/23 (87.0)	30/73 (41.1)	50/96 (52.1)
BASDAI 50			
GLM 50 mg/GLM 50 mg	51/56 (91.1)	19/37 (51.4)	70/93 (75.3)
Placebo/GLM 50 mg	28/30 (93.3)	27/66 (40.9)	55/96 (57.3)
ASAS Partial Remission			
GLM 50 mg/GLM 50 mg	29/32 (90.6)	10/61 (16.4)	39/93 (41.9)
Placebo/GLM 50 mg	17/18 (94.4)	24/78 (30.8)	41/96 (42.7)

7.2. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.3. Evaluator's conclusions on clinical 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 GLM in 197 subjects (97 on GLM, 100 on placebo) 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 EU guideline (CPMP/EWP/4891/03 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis). While only a single study has been conducted, this is considered acceptable as it complies with the EU Guideline (CPMP/EWP/2330/99 Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study). 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 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 GLM achieved an ASAS-20 response compared with those receiving placebo (71.1% versus 40.0%, p<0.0001). Results were similar for the PP population, with an even greater difference in favour of GLM observed in the 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 CHMP required this subgroup (with baseline evidence of sacroiliitis on MRI and/or screening CRP level >ULN) to be specified in the nr-Axial SpA indication for Humira in September 2012. Significant effects favouring GLM were also seen for the key secondary efficacy endpoints (ASAS-40, BASDAI 50, ASAS Partial Remission, and SPARCC MRI 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 GLM 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 GLM 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 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.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following study provided evaluable safety data:

8.1.1. Pivotal efficacy study (P07642)

In Study P07642, the following safety data were collected:

- General adverse events (AEs), serious AEs (SAEs), and vital signs were elicited by questioning and/or examination of the subject at each visit (every 4 weeks up until Week 24, then every 8 weeks until Week 60). Adverse events were presented by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.
- AEs of particular interest included:
  - An overdose of GLM (any dose higher than the dose specified in the protocol).
  - Clinically important hepatobiliary AE: defined as an elevation of ALT ≥3 x upper limit of normal (ULN) associated with total bilirubin ≥2 x ULN, irrespective of the presence of the symptoms or associated AEs, or an ALT elevation ≥3 x ULN associated with an SAE in the hepatobiliary SOC.
  - Serious infections, serious opportunistic infections and TB.
  - Malignancies.
  - Serious hypersensitivity reactions.

  - Injection site reactions.
  - Antibodies to golimumab. Serum samples were collected at baseline, Week 16, and Week 52, and were analysed using a validated enzyme immunoassay (EIA). Samples that were positive for antibodies to golimumab were further tested to determine if the antibodies were neutralizing antibodies using a validated immunoassay.

  These events were selected because they had previously been identified as events of interest in the overall golimumab program, or because of an increased risk of these events in the rheumatologic population.

- Laboratory tests included:
  - Tuberculin skin test or QuantiFERON-TB Gold test (at screening only)
  - HBV screening (at screening only)
  - Routine Laboratory (Chemistry, Haematology) (at screening, baseline, Weeks 4, 16, 20, 32, 40 and 52)
  - Serum Pregnancy test (at screening only)
  - anti-GLM antibody assessment, GLM concentration, and neutralizing antibody analysis (at baseline, Week 16 and Week 52)

Safety data for Part 1 and Part 2 were analysed separately using the All Subjects as Treated (ASaT) population. The ASaT population consisted of all randomised subjects who received at least one dose of study treatment in either Part 1 or Part 2 of the study, for the respective analyses. Subjects were analysed according to the treatment they actually received for the ASaT population. In addition, overall adverse event summaries and adverse events by SOC in Part 1 and Part 2 were provided for the OSI and non-OSI populations.

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 3 SC rheumatologic studies (AS, RA, and PsA), and versus the overall dataset derived from studies of golimumab in other indications (AS, RA, PsA, UC and asthma). The sponsor's conclusion from comparing 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.

Comment: A table comparing the overall summary of AEs in the nr-Axial SpA and AS studies was included. 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 Product Information, and that based on a comparison of these data and the safety data from Study P07642 (discussed below), safety in the nr-Axial SpA population is comparable with the known safety profile of golimumab.

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.3. Dose-response and non-pivotal efficacy studies

Not applicable.

8.1.4. Other studies evaluable for safety only

Not applicable.

8.1.5. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.2. Patient exposure

At the time of the database lock, there were 97 subjects who were exposed to GLM and 100 subjects exposed to placebo in Part 1, and 189 subjects exposed to GLM in Part 2. In Part 1, the mean duration of exposure to GLM 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 GLM 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.

8.3. Adverse events

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

8.3.1.1. Part 1

The AE profile for Part 1 of Study P07642 is summarised in Table 17, below.

Table 17: Overall summary of AEs through Week 16 (ASaT)

	Placebo	Golimumab 50mg
Treated subjects in Phase 3 SC studies of AS and nrAxSpA	100	97
Avg duration of follow-up (weeks)	16.0	15.9
Avg exposure (number of administrations)	3.9	3.9
Subjects with 1 or more adverse events	46 (46.0%)	40 (41.2%)
Subjects who discontinued study agent because of 1 or more adverse events	1 (1.0%)	2 (2.1%)
Subjects with 1 or more serious adverse events	2 (2.0%)	1(1.0%)
Deaths	0	0
Subjects with 1 or more infections	23 (23.0%)	24 (24.7%)
Subjects with 1 or more serious infections	0	0
All malignancies	0	0
Lymphoma	0	0
Melanoma	0	0
Nonmelanoma skin cancer	0	0
Other malignancies[a]	0	0
Subjects with 1 or more injection-site reactions	3 (3.0%)	0

Adverse events were reported by 87 (44.2%) of the 197 subjects who received study medication. The incidence of adverse events was numerically lower for subjects on GLM as compared to those on placebo (41.2% and 47.0%[4], respectively). The most commonly affected SOCs were: infections and infestations (24.7% for GLM versus 23% for placebo), gastrointestinal disorders (8.2% for GLM versus 15% for placebo), and nervous system disorders (10.3% for GLM versus 11% for placebo). The most common AEs by PT were: nasopharyngitis (9.3% for GLM versus 9.0% for placebo), headache (7.2% for GLM, and 6.0% for placebo), nausea (6% for placebo), oropharyngeal pain (5.2% for GLM), and influenza (5% for placebo). The majority of subjects (49/87, 56%) had mild AEs, with 33% having moderate, and 10.3% having severe AEs; the placebo group had a higher rate of mild AEs.

[4] The discrepancy in the reported number of PLC subjects with AEs in the text vs the tables is because 1 subject who had an AE on the Week 16 visit was included in the P07642 CSR, but was not included in SCS Week 16 summary table.

Table 18: Number of subjects with any AEs with frequency of ≥5% on GLM through Week 16 (Part 1) by MedDRA SOC and PT (ASaT)

	P07642	
	Placebo	Golimumab 50mg
Treated subjects in Phase 3 SC study of nrAxSpA	100	97
Avg duration of follow-up (weeks)	16.0	15.9
Avg exposure (number of administrations)	3.9	3.9
Subjects with 1 or more adverse events	46 (46.0%)	40 (41.2%)
System-organ class/preferred term		
Infections and infestations	23 (23.0%)	24 (24.7%)
Nasopharyngitis	9 (9.0%)	9 (9.3%)
Gastrointestinal disorders	15 (15.0%)	8 (8.2%)
Nervous system disorders	11 (11.0%)	10 (10.3%)
Headache	6 (6.0%)	7 (7.2%)
Skin and subcutaneous tissue disorders	6 (6.0%)	9 (9.3%)
Respiratory, thoracic and mediastinal disorders	8 (8.0%)	8 (8.2%)
Oropharyngeal pain	4 (4.0%)	5 (5.2%)

8.3.1.2. Part 2

AEs were reported by 86 (45.5%) of the 189 subjects who entered Part 2. The incidence of AEs was lower for subjects on GLM/GLM as compared to those on placebo/GLM (39.8% and 51.0%, respectively). The most commonly affected SOCs were: infections and infestations (23.7% for GLM/GLM versus 34.4% for placebo/GLM), gastrointestinal disorders (10.8% for GLM/GLM versus 12.5% for placebo/ GLM), and nervous system disorders (7.5% for GLM versus 11.5% for placebo/GLM). The most common AEs by PT were: nasopharyngitis (5.4% for GLM/GLM versus 11.5% for placebo/GLM), influenza (7.5% for placebo/GLM), headache (6.5% for GLM/GLM, and 7.3% for placebo/GLM), and upper respiratory tract infection (6.3% for placebo/GLM). The majority of subjects (50/86, 58%) had mild AEs, with 36% having moderate, and 5.8% having severe AEs; the proportions were similar in both treatment groups.

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

8.3.2.1. Part 1

A total of 30 subjects (15.2%) had clinical AEs that were determined by the investigator to be possibly, probably, or definitely related to study therapy (ADR) with an incidence that was lower in the golimumab 50 mg group (13.4%) compared to the placebo group (17.0%). The most frequently occurring ADRs in both treatment groups were in the Infections and infestations SOC with a similar incidence observed in the golimumab 50 mg and placebo groups (9 [9.3%] versus 7 [7.0%], respectively). The ADRs by PT that occurred in 2 or more subjects in either group were: influenza (GLM 2.1%, placebo 0.0%), nasopharyngitis (GLM 2.1%, placebo 4.0%), nausea (GLM 0.0%, placebo 2.0%), and cough (GLM 2.1%, placebo 0.0%).

8.3.2.2. Part 2

The incidence of ADRs was lower for subjects on GLM/GLM as compared to those on placebo/GLM (12.9% and 16.7%, respectively). The SOC with the most ADRs reported was Infections and infestations with a numerically higher incidence observed in the GLM/GLM than in the placebo/GLM group (10 [10.8%] versus 8 [8.3%], respectively). The ADRs by PT that occurred in 2 or more subjects in either group were: nasopharyngitis (GLM/GLM 2.2%, placebo/GLM 3.1%), URTI (GLM/GLM 2.2%, placebo/GLM 2.1%), headache (GLM/GLM 2.2%, placebo/GLM 1.0%), oropharyngeal pain (GLM/GLM 2.2%, placebo/GLM 0.0%), aspartate aminotransferase increased (GLM/GLM 0.0%, placebo/GLM 2.1%), injection site reaction

(GLM/GLM 0.0%, placebo/GLM 2.1%), and injection site erythema (GLM/GLM 0.0%, placebo/GLM 2.1%).

8.3.3. Deaths and other serious adverse events

8.3.3.1. Part 1

Serious AEs were reported in 3 subjects in Part 1: 2 in the placebo group (back pain and cholelithiasis) and 1 event in the GLM group (foetal death in the female partner of the male subject; conception took place prior to the first dose of golimumab 50 mg). None of the serious AEs were considered to be drug-related by the investigator.

No deaths were reported during Part 1 of the study.

8.3.3.2. Part 2

Serious AEs were reported in 5 subjects in Part 2: 3 in the placebo/GLM group (staphylococcal infection, migraine, and uterine polyp) and 2 events in the GLM/GLM group (bacterial infection and duodenitis). Two of the serious AEs were considered to be drug-related by the investigator (migraine, bacterial infection).

No deaths were reported during Part 2 of the study.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Part 1

AEs resulting in discontinuation of study therapy in Part 1 were reported in 3 subjects: 2 subjects in the GLM group (cystitis and headache) and 1 subject in the placebo group (occult blood positive). Only the event of cystitis was considered to be drug-related.

8.3.4.2. Part 2

AEs resulting in discontinuation of study therapy in Part 2 were reported in 3 subjects: 2 subjects in the placebo/GLM group (hepatitis B and rhinitis) and 1 subject (with 2 events) in the GLM/GLM group (acute tonsillitis and bacterial infection). The events of rhinitis and bacterial infection were considered to be drug-related.

8.3.5. Adverse events of Special Interest

8.3.5.1. Part 1

- Overdose: none reported.
- Clinically Important Hepatobiliary Events: none reported.
- Serious Infections, Serious Opportunistic Infections and TB: none reported.
- Malignancies: none reported (including melanoma and non-melanoma skin cancer (NMSC)).
- Serious hypersensitivity reactions: none reported.
- Injection site reactions: 3 subjects on placebo had injection site reactions - 2 events of injection site pain and 1 of injection site pruritus.
- Antibodies to Golimumab: 4 subjects receiving GLM in Part 1 tested positive for antibodies to golimumab, all of whom also tested positive for neutralising antibodies. Two of these 4 subjects had an AE: 1x vertebral artery occlusion, which was mild in intensity and resolved; 1x hives, which was moderate in intensity, not related, and resolved. None of these subjects had a hypersensitivity reaction, or discontinued the study.

8.3.5.2. Part 2

- Overdose: none reported.
- Clinically Important Hepatobiliary Events: none reported.

- Serious Infections, Serious Opportunistic Infections and TB: There were 2 subjects (1 x GLM/GLM, 1 x placebo/GLM) in Part 2 with 1 or more serious infections (as described above).
- Malignancies: none reported (including melanoma and NMSC).
- Serious hypersensitivity reactions: none reported (2 subjects had non-serious hypersensitivity reactions, both reported as allergies).
- Injection site reactions: 4 subjects on GLM had one or more injection site reactions – 2 x Injection site erythema, 1 x Injection site pain, 1 x Injection site bruising, and 2 x Injection site reaction.
- Antibodies to Golimumab: not reported for Week 52.

8.4. Laboratory tests

The proportion of subjects whose laboratory values were outside pre-specified limits for each test is discussed below

8.4.1. Liver function

8.4.1.1. Part 1

No patient in either treatment group had and ALT or AST which met the pre-specified criteria (≥100% increase and value >150 IU/L). Two patients (2.1%) on GLM had a bilirubin that met the pre-determined criteria (≥100% increase and value >1.5 mg/dL).

8.4.1.2. Part 2

Three subjects (3.2%) in the GLM/GLM group had an ALT with a ≥100% increase and value >150 IU/L, and 6 (6.5%) had a bilirubin with a ≥100% increase and value >1.5 mg/dL. No subject met both criteria.

Comment: It appears from Appendix A.133 TSFS1B12 of the Integrated Summary of Safety, that the 3 subjects with an increased ALT all had ALTs that fell in the ≥2 and < 3x ULN range. The sponsor will be asked to confirm if any subjects had and ALT or AST >3x ULN.

8.4.2. Kidney function

8.4.2.1. Part 1

No subjects in either treatment group had an increase in blood urea nitrogen (BUN) or creatinine that met pre-determined criteria.

8.4.2.2. Part 2

No subjects in either treatment group had an increase in BUN or creatinine that met pre-determined criteria.

8.4.3. Other clinical chemistry

8.4.3.1. Part 1

One subject each in the GLM and placebo groups had an elevated potassium level (Increase ≥ 0.8 and Value > 5.5). Two subjects on GLM had an elevated bilirubin (Percent increase ≥ 100 and Value > 1.5).

8.4.3.2. Part 2

Two subjects had an elevated potassium level in Part 2. One of these subjects had previously had an elevation in Part 1. Both potassium levels were normal at the last measurement. Both

subjects with an elevated bilirubin level in Part 1 had a further elevation in Part 2, and an additional 6 subjects had bilirubin elevations in Part 2 only. Five subjects had elevated bilirubin levels at the last measurement.

8.4.4. Haematology

8.4.4.1. Part 1

Two subjects on GLM (1 x lymphopaenia, 1x neutropaenia) and 2 subjects on placebo (1 x leucocytosis, 1 x eosinophilia) reported a haematology abnormality.

8.4.4.2. Part 2

Six subjects on GLM/GLM (1 x Lymphopaenia, 4 x neutropaenia, and 1 x eosinophilia) and 9 subjects on placebo/GLM (5 x neutropaenia, 4 x eosinophilia) reported a haematology abnormality.

8.5. Post-marketing experience

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

8.6. Evaluator's overall conclusions on clinical safety

In the pivotal Study P07642 to investigate the safety and efficacy of 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 GLM 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 GLM in AS and other inflammatory rheumatic diseases.

Adverse drugs reactions were reported in 13.4% of subjects on GLM and 17.0% of subjects on placebo. The most frequently reported ADRs were infections and infestations, with nasopharyngitis being the most common single event (6 subjects, 3.0%). There were few SAEs reported (3 in Part 1 [1 on GLM], and 3 in Part 2), with only 2 events considered to be drug-related by the investigator (both in Part 2, 1 x bacterial infection and 1 x migraine). Discontinuations occurred in 3 subjects in Part 1: two on GLM and one on placebo, with a further 3 subjects discontinuing during the GLM 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, TB, or malignancies.

9. First round benefit-risk assessment

9.1. 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.

9.2. 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 GLM than those receiving placebo.
- Few SAEs were reported and only 5 subjects on GLM withdrew because of an AE. While there were numerous infections reported, the percentage of subjects with one or more infections was similar in the GLM 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 placebo; 4 on GLM) 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.

9.3. First round assessment of benefit-risk balance

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

10. First round recommendation regarding authorisation

11. Clinical questions

11.1. Efficacy

5. Patients with AS based on the modified NY criteria for definite diagnosis of AS were excluded. This was based on central reading of a conventional X-ray performed at Screening. For subjects who had a sacroiliac (SI) joint X-ray performed within 3 months prior to Screening, this X-ray could be sent for central reading. If these X-rays were evaluable by central reading then these patients did not need to have a SI joint X-ray repeated at Screening. It is not known whether some of these patients may have progressed to meet the criteria for AS between the time of X-ray and study entry, and therefore should have been excluded. Please provide the number of patients whose inclusion was based on an historical SI joint X-ray, and report the length of time prior to screening when the X-ray was performed for each of these individuals.
6. The proposal to only include patients with an elevated CRP and/or MRI evidence of inflammation in the indication should address the apparent reduced efficacy in women, as it appears that this may be at least partially due to the higher proportion of females with a CRP within the normal limits. To investigate this interpretation, please provide the equivalent of Figure 11-4 from the CSR for the OSI population.

11.2. Safety

7. In the P07642 CSR the predetermined abnormality criteria for ALT and AST were a percent increase ≥ 100 and a value >150. In Part 2 of the study 3 subjects met this criterion for ALT, and it appears from Appendix A.133 TSFS1B12 of the ISS that all 3 had an ALT that fell in the ≥ 2 and < 3x ULN range. Can you please confirm if any subjects had and ALT or AST > 3x ULN.

11.3. Regulatory

8. In Table 7 of Part 2I of the RMP (Pharmacovigilance Plan) it states the final study report for P07642 is expected in November 2015. If available, please submit these data as part of the response.

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

12.1. Efficacy

12.1.1. Question 1

12.1.1.1. Sponsor response

The sponsor provided the requested information. In total, 33 subjects (16.7% of the FAS) were included in the GO-AHEAD study based on an historical SI-joint X-ray. The range of time prior to screening of these X-rays was 1 to 71 days, with a mean of 20 days and a median of 14 days. Most subjects (19/33, 58%) had X-rays performed within 2 weeks of the screening period for the majority of subjects (27/33, 82%) the X-rays were taken within 30 days of the screening

period. The sponsor commented on the slow rate of radiographic progression in axial spondyloarthritis, with radiographic outcomes in clinical trials typically measured at 2 years of follow-up.

12.1.1.2. Evaluator comment

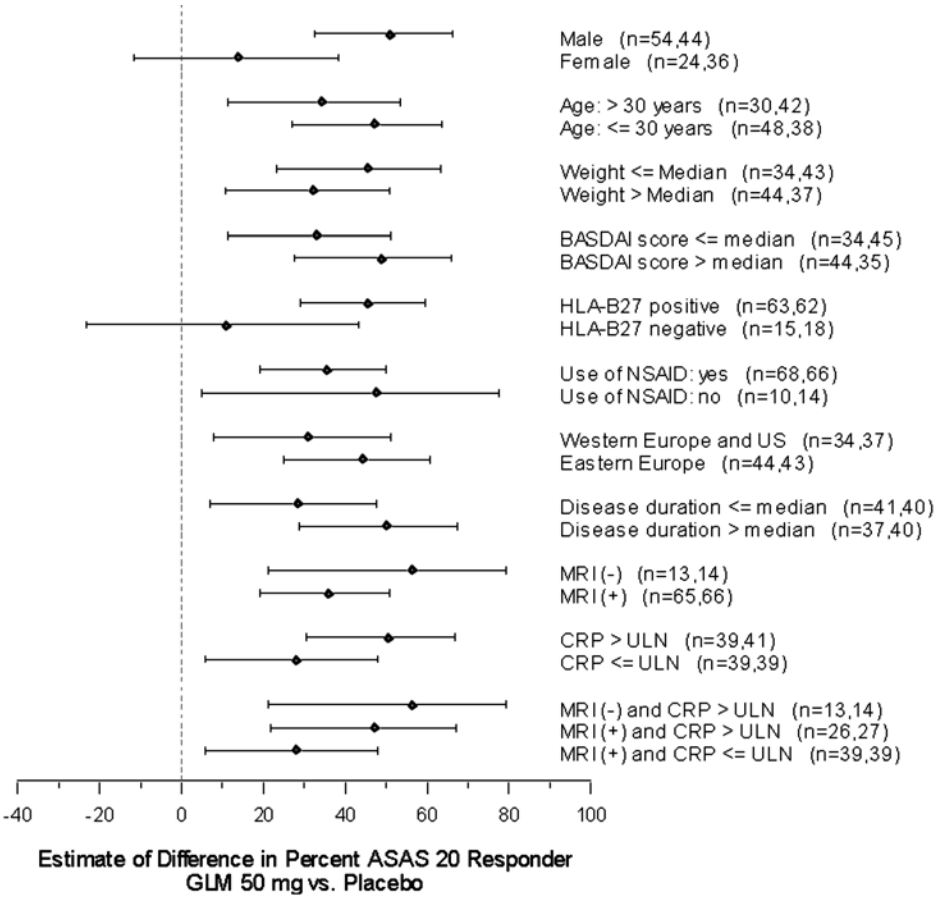
The response is acceptable.

12.1.2. Question 2

12.1.2.1. Sponsor response

The sponsor provided the requested Figure 4 (below). The OSI population excluded those subjects with both a negative MRI and a CRP ≤ ULN. After excluding these subjects, the pattern of ASAS Responder Status remained lower in females (but still favouring GLM over placebo) compared with males, and appeared somewhat improved in males.

Figure 4: Difference in percent ASAS-20 responder status at Week 16 by baseline factors point estimate and 95% confidence interval golimumab 50 mg versus placebo target population (Part 1)



12.1.2.2. Evaluator comment

Based on the persistent difference in response rates, it appears that while the CRP is important there must be other baseline factors that contribute to the lower response in females compared to males. Given that there were a number of other pre-specified demographic and baseline factors that showed a difference in ASAS 20 responder rates (for example, disease duration, HLA-B27 status, age, disease duration) it is possible that one, or more likely a combination, of these factors may contribute to the difference seen in females. In an analysis of the impact of

gender on treatment outcomes in female patients with AS[5], it was noted that females generally have an older mean age of disease onset, shorter mean time of disease duration, and a lower proportion of HLA-B27 positivity. Each of these factors in the GO-AHEAD study was associated with a lower ASAS 20 responder status. Given AS and nr-Axial SpA are considered to be subgroups of axial SpA by ASAS, it is considered likely that the differences seen with females with AS would also be seen in females with nr-Axial SpA and that therefore this might account for the lower response in females compared to males. The response is acceptable.

12.2. Safety

12.2.1. Question 3

12.2.1.1. Sponsor response

The sponsor stated that 3 subjects had an ALT ≥ 3x ULN and no subjects had an AST ≥ 3x ULN after baseline.

12.2.1.2. Evaluator comment

As none of these subjects also had a total bilirubin > 2xULN, no subject fulfilled the criteria for a Hy's Law case. The response is acceptable.

12.3. Regulatory

12.3.1. Question 4

Sponsor response

The sponsor submitted the final CSR (Report Date 12 November 2015) which presents data after all subjects had completed Week 60, compared with Week 24 in the first CSR. Treatment allocations were unblinded after subjects completed Week 24. The statistical analyses conducted for the 24-Week CSR are considered the definitive results for comparison of GLM with placebo. The Primary and Key Secondary Trial Objectives were addressed in the first (24-Week) CSR written for this study. The 60-Week CSR provides descriptive summaries of other secondary trial objectives, including efficacy results from Week 20 through Week 52, pharmacokinetic and immunogenicity results through Week 52, and safety results through Week 60.

12.3.1.1. Evaluator comment

The response is noted. An overview of the descriptive analyses of other secondary trial objectives is presented in the Appendix (not in this AusPAR). Overall, efficacy (as measured by the primary and key secondary efficacy endpoints) observed with GLM treatment at Week 16 continued to improve in GLM/GLM subjects until Week 32 and was maintained out to Week 52. In the placebo/GLM group a marked improvement in efficacy response was observed between Week 16 and Week 20 after switching to GLM at Week 16, and the response remained relatively stable thereafter. There were no new safety signals identified in the final CSR.

[5] Irene E van der Horst-Bruinsma, Debra Jeske Zack, Annette Szumski, Andrew S Koenig. Concise report: Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. *Ann Rheum Dis annrheumdis-2012-202431Published Online First: 22 December 2012 doi:10.1136/annrheumdis-2012-202431*

13. Second round benefit-risk assessment

13.1. 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 Section 9.1. The exception is that efficacy has been shown to further improve out to Week 32, and to be maintained up to Week 52.

13.2. 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 Section 9.2. Efficacy and safety results are now based on 52 and 60 weeks of data, respectively. No new safety signals identified in the final CSR.

13.3. Second round assessment of benefit-risk balance

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

14. 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.

15. References

1. Poddubnyy D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:1369–74.
2. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum. 2008 Jul;58(7):1981-91.

MRL Clinical Study Report (Synopsis), Multicenter Study: A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFα monoclonal antibody, administered subcutaneously, in subjects with active ankylosing spondylitis.

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