21 May 2015
EMA/CHMP/422136/2015
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Simponi

International non-proprietary name: GOLIMUMAB

Procedure No. EMEA/H/C/000992/II/0061

Marketing authorisation holder (MAH): Janssen Biologics B.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

abbreviation	description of abbreviated term
ADR	adverse drug reactions
AE	adverse event
ALT	alanine aminotransferase
AS	ankylosing spondylitis
ASQoL	Ankylosing Spondylitis Quality of Life Questionnaire
AST	aspartate aminotransferase
ASAS	Assessment in Spondyloarthritis international Society
ASDAS-C	Ankylosing Spondylitis Disease Activity Score CRP
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
CI	confidence interval
CRP	C-reactive protein
CSR	Clinical Study Report
DMARD	disease-modifying antirheumatic drugs
EQ-5D	EuroQol-5D Health Questionnaire
EU	European Union
FAS	Full Analysis Set
GLM	golimumab
HLA-B27	human leukocyte antigen B27
ISS	Integrated Summary of Safety
IV	intravenous
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MASES	Maastricht AS Enthesitis Score Index
MPA	Medical Products Agency
MRI	magnetic resonance imaging
nr-Axial SpA	non-radiographic axial spondyloarthritis
NSAID	nonsteroidal anti-inflammatory drug
OSI	Objective signs of inflammation (population)
PFS	pre-filled syringe
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
PSUR/PBRER	Periodic Safety Update Report/ Periodic Benefit-Risk Evaluation Report
Q4W	every 4 weeks
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAE	serious adverse event
SC	Subcutaneous(ly)

SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SE	standard error
SF-36	36-item short form health survey
SI	sacroiliac
SmPC	Summary of Product Characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	tuberculosis
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
ULN	upper level of normal
US	United States
VAS	visual analogue scale
WPAI	Work Productivity and Activity Impairment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen Biologics B.V. submitted to the European Medicines Agency on 11 November 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name:**
Simponi	GOLIMUMAB

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The Marketing authorisation holder (MAH) applied for a new indication for the treatment of non-radiographic axial spondyloarthritis (nr-Axial SpA).

Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0226/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0226/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0226/2014.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date:	11 November 2014
Start of procedure:	28 November 2014
Rapporteur's preliminary assessment report circulated on:	19 January 2015
PRAC Rapporteur's preliminary assessment report circulated on:	19 January 2015
PRAC RMP advice and assessment overview adopted by PRAC on:	12 February 2015
Rapporteur's updated assessment report circulated on:	20 February 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 February 2015
MAH's responses submitted to the CHMP on:	19 March 2015
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 April 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 April 2015
PRAC RMP advice and assessment overview adopted by PRAC on:	7 May 2015
Rapporteur's updated assessment report on the MAH's responses circulated on:	14 May 2015
CHMP opinion:	21 May 2015

2. Scientific discussion

2.1. Introduction

Golimumab is a human monoclonal IgG1 antibody that binds to both soluble and trans-membrane forms of tumor necrosis factor alpha (TNFα) and inhibits TNFα bioactivity. Golimumab is classified according to the ATC Classification System as a TNFα inhibitor. Other members of this therapeutic class include infliximab, etanercept, adalimumab, and certolizumab pegol.

Simponi is approved for the treatment of inflammatory diseases, including ankylosing spondylitis (AS), rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC).

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.

The Assessments in Spondyloarthritis International Society (ASAS) criteria for classification of **Axial SpA**, are; Back pain of ≥3 month duration at age of onset <45, and either of the three is true: 1. The subject has active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA and in addition at least one of the below clinical features; 2. The subject has definitive sacroiliitis (grade ≥2 bilaterally or ≥3 unilaterally) on x-ray and in addition at least one of the below clinical features; 3. The subject is HLA B27 positive and has at least two further of the below clinical features.

The clinical features include: HLA B27 positivity;-inflammatory back pain; arthritis; enthesitis; uveitis; dactylitis; psoriasis; Crohn's/colitis; elevated CRP; good response to NSAIDs in the past; family history for SpA.

nr-Axial SpA is thus a subgroup of Axial SpA, consisting of those who do not meet criterion # 2 above.

The modified NY criteria for AS (mNY) require x-ray findings of sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally. In addition, at least 1 of the 3 following clinical criteria must be fulfilled:

- Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
- Limitation of motion of the lumbar spine in the sagittal and frontal planes.
- Limitation of chest expansion relative to normal values correlated for age and sex.

Patients with nr-Axial SpA have substantial disease burden, similar to patients with AS, who have relatively longer disease duration. 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 year (Sampiano-Barros et al, Clin Rheumatol, 2001) The Assessment in Spondyloarthritis international Society (ASAS) has recommended use of TNFα antagonists in patients with active AS or nr-Axial SpA, following failure of at least 2 NSAIDs over a 4 week period or intolerance to such agents (van der Heijde et al, Ann Rheum Dis 2011). TheTNFα antagonists adalimumab, certolizumab, and etanercept are approved for the treatment of nr-Axial SpA.

With this variation, the MAH sought to add the following new indication to the product information:

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

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

The proposed indication for golimumab for the treatment of nr-Axial SpA is supported by the results of an on-going single, multicentre, randomized, double-blind, placebo-controlled study (P07642).

This submission focuses on:

- Efficacy data through Week 16 (the placebo-controlled period) and through Week 24 from P07642. The main focus is on 16-week data describing the efficacy of golimumab in the improvement of signs and symptoms of disease, spinal mobility, inflammation as measured by MRI, physical function, and health-related quality of life. Data from the open label period through Week 24 demonstrate the persistence of treatment effect.
- PK and immunogenicity data through Week 16 from P07642
- Safety data through the last data cut-off (06 May 2014) from P07642 is described comprehensively in 3 presentations:

1. Comparisons of data from the P07642 study and the combined AS studies (C0524T09 and C0524T29) dataset.
2. Comparisons of data from the P07642 study and the large datasets derived from the combined Phase 3 SC rheumatologic studies (AS, RA, and PsA).
3. Comparisons of data from the P07642 study and overall dataset derived from the large, long term safety database for golimumab in AS, RA, PsA, UC and asthma studies as detailed in section 2.5 (Safety).

There is no specific guideline for the development of medicinal products for the treatment of nr Axial SpA. The clinical study supporting this extension of indication is in line with the Guideline on clinical investigation of medicinal products for the treatment of AS (CPMP/EWP/4891/03) with respect to study design, main efficacy endpoint, and secondary endpoints.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Trial ID	Phase	Country	Tri	Trial design	Dosing regimen	Trial population	Subject exposure
8259-006 [P006]	3b	Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Italy, Russia, Slovakia, Spain, Turkey	A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Golimumab Administered Subcutaneously in Subjects with Active Axial Spondyloarthritis (Phase 3b, Protocol No. P07642, also known as MK-8259-006-02).	A Phase 3b, two-part, randomized, parallel-group, multi-site, doubleblind, placebo-controlled trial with an open-label extension in adults aged 18 to 45 years old with active non-radiographic axial	Arm A (Part 1) golimumab 50-mg SC at Baseline, at Weeks4, 8, and 12 Arm B (Part 1) placebo SC at Baseline, at Weeks 4, 8, and 12 Part 2 golimumab 50-mg SC starting at week 16, and then every 4 weeks until	Males/females Age: 18-45 with active non-radiographic axial SpA (nr-Axial SpA)	Arm A (Part 1) golimumab 50- mg: 97 subjects Arm B (Part 1) placebo: 100 subjects Part 2 golimumab 50-mg:189

2.3.2. Pharmacokinetics

The PK of golimumab was evaluated in the Phase 3 study (Study P07642).

Samples for golimumab concentration analysis were collected at Baseline (Week 0) and Week 16 before the administration of study medication. All samples from subjects randomized to placebo showed golimumab concentrations <0.039 µg/mL, the lower limit of quantification for the assay.

Serum golimumab concentrations at Week 16 were evaluated in 2 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 >ULN.

Median golimumab concentrations at Week 16 for the OSI population were the same to the all treated population (0.8 and 0.8 µg/mL, respectively).

An analysis of trough serum golimumab concentrations by weight quartiles was performed for Study P07642 and a trend in lower concentrations for subjects in the higher weight quartiles were observed.

Study C0524T09 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab 50 mg or 100 mg administered as SC injections Q4W in adult subjects with active AS.

Trough serum golimumab concentrations achieved steady state by Week 12 and were approximately proportional to dose after SC administrations of golimumab 50 mg Q4W and 100 mg Q4W. At Week 12, the median steady-state trough concentrations were 0.6 µg g/mL and 1.1 µg g/mL in the 50 mg and 100 mg groups, respectively. Serum trough golimumab concentrations from Week 52 were generally maintained through Week 256 and were similar to the observed median serum golimumab concentrations observed at Week 24.

An analysis of trough serum golimumab concentrations by weight quartiles performed for the original submission and a trend in lower concentrations for subjects in the higher weight quartiles were observed.

Impact of weight

In P07642, the effect of body weight on PK was examined by weight quartile and body-weight cut at 100 kg (Table 1). When serum golimumab concentrations were evaluated by weight quartiles, subjects in the higher weight quartile tended to have lower serum concentrations than those in the lower weight quartile. This trend was also seen in similar analyses conducted for the 5 Phase 3 AS, RA, and PsA studies. Subjects with body weights >100 kg tended to have lower serum golimumab concentrations than subjects with body weights ≤100 kg. Due to the small number of golimumab-treated subjects weighing >100 kg (n=6) in P07642, weight-based PK/efficacy analyses were not performed. However, in previous efficacy-by-body weight analyses done for the rheumatological indications, a trend toward a decreased response rate with increasing weight was observed when comparing subjects who weighed ≤100 kg with those weighing >100 kg.

Table 1 Summary of Steady-state Serum Golimumab Concentrations (µg/mL) after 50 mg golimumab SC at Week 16 by 100kg weight cut-off; Subjects Treated With Golimumab in Study P07642

	Golimumab		
	≤100kg	>100kg	Overall
Study P07642 (nr-Axial SpA)			
50 mg SC golimumab			
N	86	6	92
Mean (SD)	0.95 ± 0.73	0.59 ± 0.49	0.93 ± 0.72
Median	0.77	0.66	0.77

SC=subcutaneous; SD-standard deviation.

Impact of immunogenicity

In Study P07642, antibodies to golimumab were evaluated at Week 0 and Week 16. The overall incidence of antibodies to golimumab in subjects with nr-Axial SpA in P07642 through Week 16 was 4.3% (4/93). A similar result was observed in subjects with AS in C0524729 study, where antibodies to golimumab were evaluated at Week 0 and Week 24. The incidence of antibodies to golimumab was 5.7% (5/87). For subjects who were positive for antibodies to golimumab, 100% were positive for neutralizing antibodies through Week 16 and Week 24 in P07642 and C0524T09, respectively. Serum golimumab concentrations were generally low in those subjects who were classified as positive for antibodies to golimumab. All subjects in P07642 who were positive for antibodies to golimumab (and neutralizing antibodies), sufficient efficacy was observed despite their exposures being at the lower limit of quantification when measured at Week 16. This suggested that development of immunogenic response had little impact on efficacy.

2.3.3. Discussion on clinical pharmacology

The pharmacokinetics of golimumab has been described previously in healthy subjects and in patients with RA as described in the product information. In summary, the median time to reach maximum serum concentrations ranged from 2 to 6 days following subcutaneous administration. Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Golimumab exhibits approximately dose proportional PK. The average volume of distribution (V) has been shown to be 115 mL/kg and systemic clearance (CL) of golimumab was estimated to be 6.9 mL/day/kg. Terminal half-life was estimated to be approximately 12 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. Population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

The PK of golimumab was evaluated in the Phase 3 study (Study P07642) in patients with nr-Axial SpA. PK samples for serum golimumab concentration were collected from all subjects at Day1, Week 16 and Week 52. The same serum samples were used for the measurement of golimumab concentrations and detection of antibodies to golimumab. Serum samples were analyzed for golimumab concentrations using a validated electrochemiluminescent immunoassay (ECLIA) on a Meso Scale Discovery (MSD) Platform. The lower limit of quantification (LLOQ) with the MSD platform was 0.039 µg/mL at a 1:5 dilution. Serum samples for the detection of antibodies to golimumab were analyzed using a validated enzyme immunoassay (EIA). The bioanalytical methods have been used in previous SC studies and therefore been described in detail in previous submissions.

The steady-state median golimumab concentration for all subjects treated with golimumab 50 mg was 0.8 µg/mL. These concentration values were consistent with those observed in AS Study C0524T09 and were within the range of steady-state golimumab concentrations observed in the other rheumatological indications. The results suggested that golimumab exposure is similar between the nr-Axial SpA population and populations in other rheumatologic indications, thus supporting consistency in posology across the rheumatologic indications.

Due to similarity in the median steady-state concentrations at Week 16 between nr-Axial SpA and AS, and dose linearity previously established for SC golimumab from 50 mg to 400 mg, it is expected that this trend in efficacy seen in the rheumatological indications may also occur in nr-Axial SpA. Therefore, the MAH proposed posology consistent with the approved posology for the other rheumatologic indications. This was agreed by the CHMP.

Antibodies to golimumab were evaluated at Week 0 and Week 16 for Study P07642. The overall incidence of antibodies to golimumab in subjects with nr-Axial SpA in P07642 through Week 16 was 4.3% (4/93). This incidence was stated to be similar to the incidence in subjects with AS in Study C0524T09 through Week 24 (5.7%, 5/87) and in subjects with other rheumatologic diseases.

In P07642, the 4 subjects positive for antibodies to golimumab were also positive for neutralizing antibodies through Week 16. Serum golimumab concentrations were below the limit of detection at Week 16 for all 4 subjects.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of golimumab has been adequately studied to support the use in patients with nr-Axial SpA. The correlation between exposure and weight appears to be similar to that in previously studied patient populations and the proposal regarding dosing in patients weighing >100 kg is adequately supported.

2.4. Clinical efficacy

2.4.1. Main study

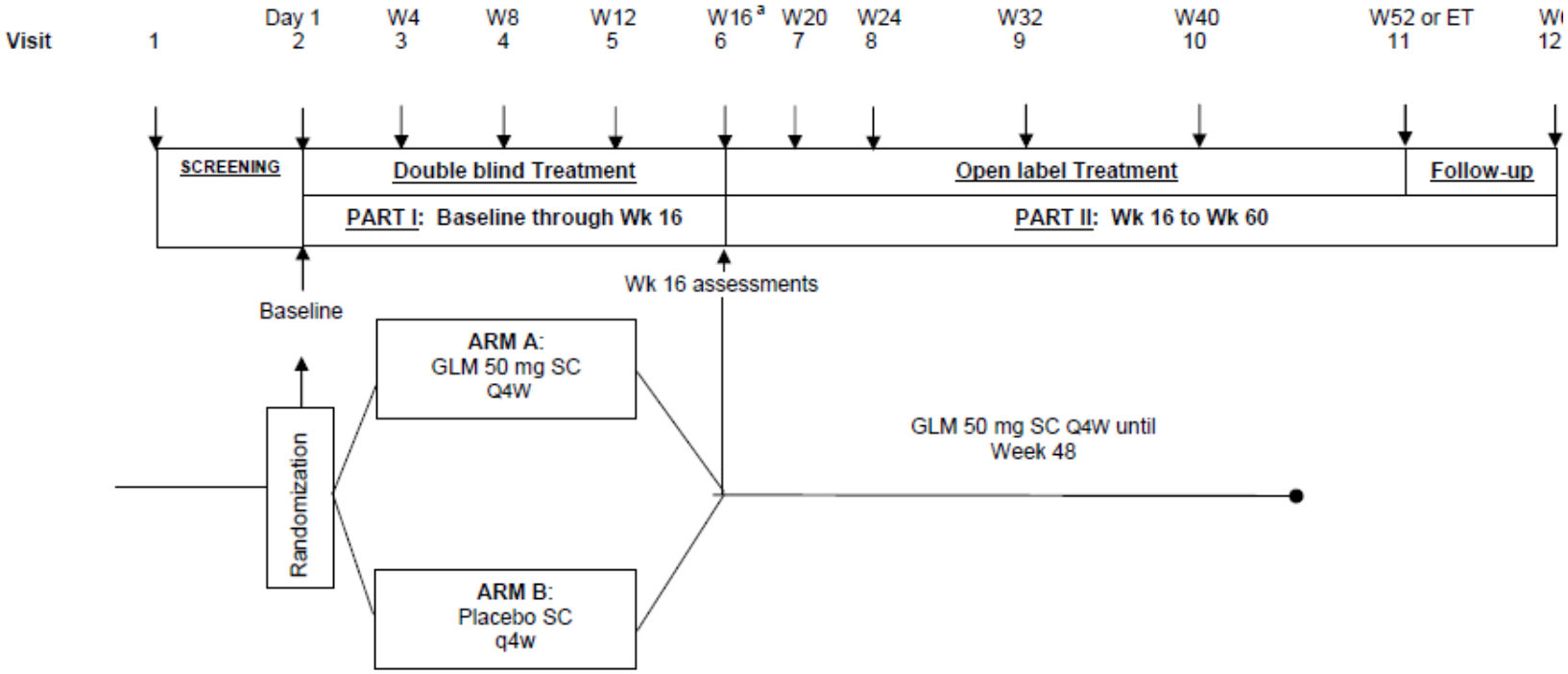
Study P07642: A Multicenter, Randomized, Double-blind, Placebo controlled Study of the Effect of Golimumab (GLM) Administered Subcutaneously (SC) in Subjects with Active Axial Spondyloarthritis (SpA) (Phase 3b, Protocol No. P07642, also known as MK-8259-006-02, and as GOAHEAD).

Methods

P07642 is a multicenter, randomized, double-blind, placebo-controlled study of golimumab administered subcutaneously in subjects with nr-Axial SpA.

The study included a 16-week double-blind, placebo-controlled period, followed by a 44-week open-label treatment period (Part 2), which is on-going. The total duration of the study is 60 weeks. The study schema for P07642 is presented in Figure 1.

Figure 1: Study P06742 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.

Study participants

Main inclusion criteria

- Each subject must be ≥18 to≤45 years of age.
- Physician's diagnosis of active Axial SpA with disease duration ≤5 years, and chronic back pain of ≥ 3 month duration.

  Note: disease duration is defined as the length of time since symptom onset.
- Each subject must meet either criterion "a" or "b" as adopted from ASAS classification criteria:

  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:

     - 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; (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;

OR

b) HLA-B27+ gene and 2 or more of the following spondyloarthritis characteristics:

- Inflammatory back pain, see definition above
- Arthritis diagnosed by a physician;
- Enthesitis (heel, definition above) diagnosed by a physician
- Dactylitis;
- Psoriasis diagnosed by a physician;
- IBD diagnosed by a physician
- History of uveitis confirmed by an ophthalmologist;
- Good response to NSAIDs;
- Family history for SpA
- Elevated CRP (based on central lab values).

- High disease activity at Screening and Baseline of both a total back pain evaluation of ≥40 mm and a BASDAI score of ≥ 40 mm on a VAS of 0-100 mm.
- *Either* an inadequate response, as assessed by the investigator to 30 days of continuous therapy with maximal recommended daily doses of at least one NSAID,

  or must be unable to receive a full 30-day maximal NSAID therapy because of intolerance, toxicity, or contraindications to NSAIDs.
- If using NSAIDs, each subject must be on a stable regular daily dose for at least 30 days prior to Screening and the dose of NSAIDs is expected to remain the same through Week 16.

Exclusion criteria of note were:

- The subject has bilateral sacroiliitis Grade 2 or unilateral sacroiliitis Grade 3 or Grade 4 on conventional X-rays (i e, excluding New York modified criteria) based on central reading at Screening.
- The subject has ever received TNF-α targeted therapy or any biological agents,

Treatments

This study randomized 198 subjects in a 1:1 ratio to either the golimumab treatment arm (Arm A, 50mg SC Q4W) or the placebo treatment arm (Arm B). The 50 mg SC Q4W dose regimen was selected for evaluation in the nr-Axial SpA (P07642)study to be consistent with the approved regimen for the treatment of other rheumatologic diseases (RA, PsA, and AS) globally. Precedence for this approach exists with the anti-TNF inhibitors etanercept, adalimumab and certolizumab, which all dose nr-Axial SpA patients with the same dose as AS patients.

Subjects were allowed to remain on a stable daily dose of NSAIDS during this study as long as this dosage was initiated at least 30 days prior to Screening. A new NSAID could not be initiated until Week 16; however NSAIDs could be initiated after Week 16 at the investigator's discretion. In addition, the following medications could be initiated after Week 16 at the investigator's discretion: methotrexate, sulfasalazine, or hydroxycholoroquine. Intra-articular, tendon sheath, or bursal corticosteroid injections

in no more than 2 affected sites were allowed after Week 16. Prohibited medications during the study are displayed in the table below.

Table 2: Medications, Supplements, and Other Substances Prohibited During the P07642 Study

Disease modifying anti-rheumatic drugs such as but not limited to:
Methotrexate *
Sulfasalazine *
Leflunomide
Hydroxychloroquine *
Steroids (oral, parenteral)[1]
Cyclosporine
Mycophenolate mofetil
Azathioprine
Live vaccinations
Investigational medications
Drugs of abuse/recreational use of drug
Bacille Calmette-Guerin (BCG) vaccination
TNF-α targeted therapy or any biological agents, including but not limited to infliximab, etanercept, adalimumab, alefacept or efalizumab, rituximab, or natalizumab.
Cytotoxic drugs, including but not limited to chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents.

* These medications could be initiated after Week 16.

[1] Intra-articular, tendon sheath, or bursal corticosteroid injections in no more than 2 affected sites were allowed after Week 16 of the study.

Objectives

Primary Efficacy Trial Objective: To evaluate the effect of golimumab 50 mg compared to placebo in the treatment of active axial SpA, as measured by the proportion of subjects achieving Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 16.

Primary Safety Trial Objective: To demonstrate the safety and tolerability of GLM 50 mg through Week 16 in the active axial SpA population.

Key Secondary Trial Objectives: (1)To evaluate the treatment effect of golimumab 50 mg compared to placebo as measured by the proportion of subjects achieving ASAS 40 response at Week 16. (2)To evaluate the treatment effect of golimumab 50 mg compared to placebo as measured by the proportion of subjects who achieve Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 response at Week 16. (3)To evaluate the treatment effect of golimumab 50 mg compared to placebo as measured by the proportion of subjects who achieve ASAS partial remission at Week 16. (4)To evaluate the treatment effect of golimumab 50 mg compared to placebo by the change in the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SI joints score from Baseline to Week 16.

Outcomes/endpoints

The **primary endpoint** was proportion of subjects achieving ASAS 20 response at Week 16.

ASAS-20 is defined as meeting both 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 morningstiffness)

2. Absence of deterioration from Baseline (≥20% and an absolute change of ≥10 mm) in the potential remaining domain.

Key **secondary endpoints** were the proportion of subjects who achieved

- ASAS 40 response at Week 16,
- BASDAI 50 response at Week 16
- ASAS Partial Remission at Week 16
- Change from baseline to Week 16 in the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SI joints score

The **BASDAI** is a validated self-reported instrument which consists of six 10-unit horizontal NRSs to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week. The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. **BASDAI 50** response is defined as improvement by at least 50% from baseline in BASDAI

ASAS Partial Remission is defined as a VAS score of less than 20mm in each of the 4 domains of ASAS 20

The **other secondary efficacy variables** of P07642 were:

- Change in BASFI from Baseline to Week 16, 24, and 52;
- Change in BASMI from Baseline to Week 16; 24, and 52
- Change in CRP from Baseline to Week 16, 24, and 52
- Proportion of subjects achieving ASAS 5/6 at Week 16, 24, and 52
- Change in ASDAS-C from Baseline to Week 16, 24, and 52
- Proportion of subjects achieving low ASDAS-C (<1.3) week 16, 24, and 52
- ASAS 20 response at Week 8, 12, 24, and 52
- ASAS 40 response at Week 24, and 52
- Proportion of subjects achieving BASDAI 50 at Week 24 and 52
- Proportion of subjects in ASAS partial remission at Week 24 and 52
- Change in SF-36 from Baseline to Week 16 and 52
- Change in ASQoL from Baseline to week 16 and 52
- Change in swollen and tender joint count from Baseline to Week 16, 24, and 52
- Change in chest wall expansion from Baseline to Week 16, 24, and 52; Change in EQ-5D from Baseline to Week 16 and 52
- Change in WPAI from Baseline to Week 16 and 52
- Patient's Global Disease Assessment VAS, Total Back Pain VAS and Nocturnal

- Pain VAS from Baseline to Week 16, 24 and 52
- Change in Physician's Global VAS from Baseline to Week 16, 24 and 52
- Change in MASES Index from Baseline to Week 16, 24 and 52

The **BASFI** (Bath Ankylosing Spondylitis Functional Index) is the function domain of ASAS measures. is reported as a mean (VAS, 0 to 10 cm) of 10 questions, 8 of which relate to the functional anatomy of the subject and 2 of which relate to the subject's ability to cope with everyday life.

The **BASMI** is a score comprising 5 measures of hip and spinal mobility:

1. Tragus-to-wall
2. Lumbar flexion (modified Schober test)
3. Cervical rotation
4. Lateral lumbar side flexion
5. Maximal intermalleolar distance.

The 5 continuous measurements are used in conjunction with a scoring system to obtain a score on a scale of 0 to 10. The final BASMI score is the mean of the 5 scores. The higher the score, the more severe the patient's limitation of movement.

ASAS 5/6 is defined as a 20% improvement in any 5 of the following 6 domains: pain (VAS 0 to 10 cm), patient global (VAS 0 to 10 cm), function (BASFI score), morning stiffness (BASDAI, average of questions 5 and 6), CRP, and spine mobility (lumber side flexion).

The **ASDAS-C** is a composite index to assess disease activity in AS. It combines the following 5 disease activity variables into a single score: back pain, duration of morning stiffness, patient global score, peripheral pain/swelling, and CRP. An ASDAS-C score of < 1.3 has been defined as inactive disease or clinical remission.

The **WPAI** measured time missed from work, impairment of work, and impairment of regular activities due to overall health and symptoms. The WPAI is assessed relative to measures of general health perceptions, role (physical), role (emotional), pain, symptom severity, global measures of work, and interference with regular activity.

The **MASES** is an index to measure enthesitis and the evaluation consists of measures at 13 sites, which are scored as 0 or 1 (0 – non tender, 1 tender). It is the sum of all site scores (from 0 to13).

Sample size

Study P07642 was expected to randomize approximately 200 subjects.

For the primary endpoint, with the planned sample size of 100 subjects per group, there is at least 95% power to detect a 26% treatment difference between golimumab 50 mg and placebo (2-sided, overall a=0.050), assuming the true response rate for the placebo group is 25%. The placebo response rate was estimated based on the pivotal golimumab study in AS.

Randomisation

One-hundred and ninety-eight subjects were randomized in a 1:1 ratio to either the golimumab treatment arm (Arm A) or the placebo treatment arm (Arm B). 197 subjects were treated.

Subjects were stratified based on whether they had evidence of sacroiliitis (active inflammation) on MRI of the sacroiliac joint (yes/no) and CRP level (≤ ULN/ > ULN [0.9mg/dL]). Subjects without evidence of sacroiliitis on MRI were limited to 50% of the total enrolled population. Subjects with a normal CRP level at screening (according to the central lab) were limited to 60% of total enrolled.

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. Readers were blinded to treatment assignment, clinical information, and results of investigator readings. Stratification for presence of MRI sacroiliitis at screening based on ASAS MRI criteria18 was undertaken for subjects not meeting modified New York criteria. 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. Scoring of the SI joints utilized the SPARCC scoring system. Discrepancies between the two readers were adjudicated by a third reader.

Blinding (masking)

Part 1 was a double-blind period, with in-house blinding. The investigator, study nurse, study participant, and sponsor personnel remained blinded to the treatment group assignments. An Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS) was used to maintain the blind.

Data that could potentially unblind the treatment assignment (i.e., CRP values and MRI scores) were masked prior to unblinding.

Part 2 was open-label.

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. Readers were blinded to treatment assignment, clinical information, and results of investigator readings. Stratification for presence of MRI sacroiliitis at screening based on ASAS MRI criteria18 was undertaken for subjects not meeting modified New York criteria. 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. Scoring of the SI joints utilized the SPARCC scoring system. Discrepancies between the two readers were adjudicated by a third reader.

Statistical methods

Efficacy Analysis of the Primary Endpoint

The primary efficacy endpoint, the proportion of ASAS 20 responders at Week 16, using the FAS population was evaluated using the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes or no) and screening CRP level (≤ULN/ >ULN [0.9 mg/dL]) as the stratification factors.

Two supportive analyses were performed on the primary endpoint. One used the Per-Protocol Population and the other considered subjects who discontinued due to an AE as non-responders.

Efficacy Analysis of Secondary Endpoints

Part 1

The binary response type secondary variables were evaluated in the same way as the primary variable.

The change from Baseline in the SPARCC MRI SI joint score was compared between golimumab 50 mg and placebo using the Mann-Whitney test.

Other continuous secondary variables were evaluated using a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger. The analysis model included terms for treatment, week, baseline evidence of sacroiliitis on MRI (yes or no), screening CRP level (≤ULN/ > ULN) and treatment by

week interaction. The treatment difference in terms of mean change from baseline at Week 16 was estimated and tested from this model. An unstructured covariance matrix was used to model the correlation among repeated measurements.

If the continuous variables were not considered to be normally distributed, then a nonparametric test, such as Mann-Whitney or Wilcoxon rank sum test was performed.

Part 2

Subjects who successfully completed Part 1 (Weeks 0-16), were eligible to participate in Part 2 (Weeks 16-60) of the trial. All subjects in Part 2 received golimumab 50 mg SC at Week 16 (after completion of all visit assessments), and every 4 weeks thereafter, with the final dose administered at Week 48. A final efficacy assessment will be performed after Week 52 as well as a final safety assessment at Week 60, 12 weeks after the last dose of study treatment is targeted to be administered.

To assess the long-term treatment effect, descriptive statistics of the efficacy endpoints for the FAS population (counts and percentages for binary response type variables; mean, standard deviation [SD], median, minimum and maximum for continuous variables) were tabulated by treatment group (golimumab 50 mg/ golimumab 50 mg, placebo/ golimumab 50 mg) at each visit.

Multiplicity adjustment for Type I error control was implemented in the Part 1 analyses using a closed testing procedure to control the overall α level at 0.05 for the primary and key secondary endpoints. The primary endpoint was tested first and if significant, was followed by tests of the key secondary endpoints in the order presented. Efficacy results will be considered statistically significant after consideration of the strategy for controlling the Type I error. All statistical tests were conducted at the alpha=0.05 (2-sided) level.

Both the multiplicity method and the primary and key secondary endpoint analyses were prespecified in the protocol.

Efficacy Analysis Populations

The primary (overall) population for efficacy analyses is called the efficacy Full Analysis Set (FAS) population (also referred to as the All Treated [AT] population; n=197 in Part 1); the safety population consists of all subjects as treated (n=197 in Part 1). A per protocol population is also defined (n=174 in Part 1). The subgroup population consisting of subjects with evidence of sacroiliitis on MRI and/or screening CRP level >upper limit of normal is referred to as the OSI population (n=158) and is the same subgroup for both efficacy and safety analyses. Efficacy analysis populations in P07642 are outlined in Table 3.

Table 3 Efficacy Analysis Populations

Analysis Set Name	Study Phase	Placebo	GLM 50 mg	Total	Definition
Overall Population, All Treated (AT), Full Analysis Set (FAS)	Part 1	100	97	197 (100%)	All randomized subjects who received at least 1 dose of study treatment during Part 1 of the study. If subjects received incorrect treatment throughout Part 1 they were analyzed according to their randomized treatment assignment.
	Part 2 (through Week 24)	96	93	189	All randomized subjects who received at least 1 dose of study treatment during Part 2 of the study.

Table 3 Efficacy Analysis Populations

Analysis Set Name	Study Phase	Placebo	GLM 50 mg	Total	Definition
Overall Population, Per Protocol (PP)	Part 1	90	84	174	Excludes 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 may substantially affect or confound the measures of efficacy or the intended claims for the compound.
Objective Signs of Inflammation (OSI) Population	Part 1	80	78	158 (80%)	The subset of FAS subjects who had elevated CRP and/ or MRI evidence of sacroiliitis at randomization.
Non-OSI Population	Part 1	20	19	39 (20%)	The subset of FAS subjects who had normal CRP and no MRI evidence of sacroiliitis at randomization.

Missing Data Imputation Strategy

For the ASAS related endpoints at Week 16 (ASAS 20, ASAS 40, ASAS 5/6, and ASAS partial remission), if subjects were missing all of the ASAS components at Week 16, they were considered to not have achieved the primary endpoint. Zero-divisor and component-wise missing data rules also applied.

For BASDAI 50, if the subject had no observation at Week 16, then the last non-missing observation prior to Week 16, including the Baseline value, was carried forward to Week 16. The missing data at other timepoints, such as Week 24 and Week 52, were imputed similarly.

In case of missing BASFI responses at a specific timepoint, the mean score was based on the available data from a minimum of 5 questions. In case of missing BASMI responses at a specific timepoint, the mean score was based on the available data from a minimum of 3 components. Otherwise, BASFI or BASMI were considered missing at that timepoint. Only observed data were used in the analyses and summaries, no missing data were imputed.

In addition, subjects who met any one of the treatment failure criteria prior to Week 16 had the change from Baseline set to 0 at Week 16. No treatment failure rule was used for BASFI or BASMI at timepoints after Week 16.

ASDAS-C was calculated if all the components were non-missing. Otherwise, ASDAS-C was considered missing. Only observed data were used in the analyses and summaries, no missing data were imputed.

Component-wise missing data rules:

1. For any ASAS component, if the component value is missing from baseline through Week 16, then 0% will be assigned for the percent improvement from baseline of that component;

2. If the subject has a baseline value but no observation at Week 16, then the last non-missing observation prior to Week 16, including the baseline value, will be carried forward to Week 16;

3. If the baseline value is missing for a component, but a post-baseline value is observed prior to or at Week 16, then the median component value from all subjects with baseline data in the same stratum (defined based on the baseline MRI and CRP) will be used to impute the baseline value.

The missing data at other timepoints, such as Week 24 and Week 52 will be imputed similarly as described above.

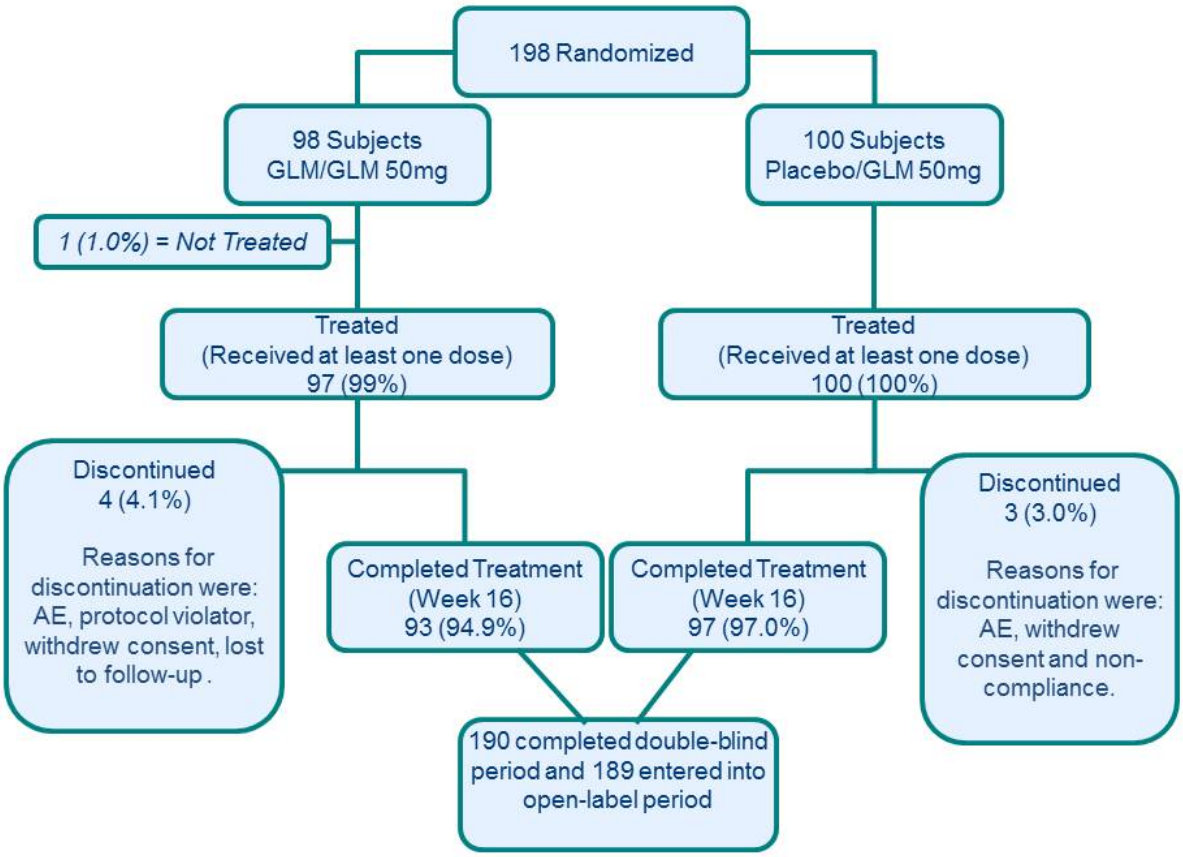
For all other continuous endpoints only observed data were used in the analyses and summaries, no missing data were imputed.

Results

Participant flow

Of the 393 subjects screened for inclusion in the study, a total of 198 subjects were randomized, with 98 assigned to receive golimumab 50 mg and 100 assigned to placebo. One hundred and ninety of the 198 (96.0%) randomized subjects completed the placebo-controlled period of the study (Part 1 through Week 16).

Figure 2: P07642 Study Subject Disposition Part 1



At the time of the database lock, 187 subjects (94.4%) had completed treatment through Week 24; 155 subjects (78.3%) had completed treatment through Week 52 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.

Recruitment

Subjects were randomized at 52 study centers in 13 countries worldwide (Western Europe, Eastern Europe and North America). Enrollment at each study center ranged from 1 to 12 subjects.

Conduct of the study

Protocol violators were identified prior to the first unblinding of the database and were excluded from the Per-Protocol analysis. The Per-Protocol population excluded 23 subjects based on a set of prespecified criteria; 13 from the golimumab 50 mg group and 10 from the placebo group. Excluded subjects included 8 (4%) subjects with violations on the exclusion and inclusion criteria, 9 (4.5%) subjects with low medication compliance or early discontinuation from Part 1 (subjects did not receive all 4 doses of study medication), 4 (2%) subjects with use of prohibited medications or unstable NSAID use (change in dose, initiation of a new NSAID or discontinuation of NSAID)

One subject was identified as not meeting inclusion criterion 3 for nr-Axial SpA diagnosis because the subject did not have sacroiliitis on MRI and was HLA-B27 negative. This was not discovered until after the data base lock, therefore, 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

Of the 198 randomized subjects, 57% were men. All subjects were White, with an average age of 31 years. Demographic and subject characteristics were generally similar between the treatment groups; however, there was a numerically higher proportion of women in the placebo (48.0%) than in the golimumab group (37.8%).

Baseline disease characteristics were also similar between treatment groups and indicative of a population with nr-Axial SpA. More than 80% of subjects were HLA-B27 positive (82.7% in the golimumab 50 mg group, 82% in the placebo group). Mean BASDAI scores of 6.6 cm in the golimumab 50 mg group and 6.4 cm in the placebo group were consistent with substantial disease activity. Mean Ankylosing Spondylitis Disease Activity Score CRP (ASDAS-C) scores were 3.6 and 3.5 in the golimumab and placebo groups, respectively. Two thirds of subjects had a positive MRI (evidence of sacroiliitis on the screening; 67.3% in the golimumab group, 66.0% in the placebo group), and 40.8% of subjects in the golimumab group and 41% in the placebo group had elevated CRP (mean 1.52 mg/dL, golimumab; mean 1.29 mg/dL, placebo). Elevated CRP was defined as CRP above the central laboratory upper limit of normal (0.9 mg/dL).

Table 4: Summary of Demographic and Disease Characteristics All Randomized Subjects

	GLM 50mg		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	7.2	

Table 4: Summary of Demographic and Disease Characteristics All Randomized Subjects						
	GLM 50mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Median	29.0		32.0	32.0	30.0	
Range	18 to 46 [1]		18 to 45	18to 45	18 to 46	
Race						
White	98	(100.0)	100	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)
Region						
Eastern Europe	52	(53.1)	53	(53.0)	105	(53.0)
Western Europe and US	46	(46.9)	47	(47.0)	93	(47.0)
Height (cm)						
Subjects with data	98		100		198	
Mean	173.0		172.1		172.6	
SD	9.8		9.5		9.6	
Median	173.5		171.3		172.0	
Range	153.0 to 196.0		152.0 to 195.0		152.0 to 196.0	
Weight (kg)						
Subjects with data	98		100		198	
Mean	76.8		74.4		75.6	
SD	15.5		15.7		15.7	
Median	78.5		74.2		76.0	
Range	45.0 to 115.0		43.4 to 124.0		43.4 to 124.0	
BMI (kg/m^2)						
Subjects with data	98		100		198	
Mean	25.6		25.1		25.3	
SD	4.7		4.9		4.8	
Median	25.2		25.0		25.1	
Range	18.0 to 43.2		16.5 to 41.9		16.5 to 43.2	
Screening C-Reactive Protein (CRP)						
<= Upper Limit of Normal (0.9mg/dL)	58	(59.2)	59	(59.0)	117	(59.1)
> Upper Limit of Normal (0.9mg/dL)	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)

Table 4: Summary of Demographic and Disease Characteristics All Randomized Subjects						
	GLM 50mg		Placebo		Total	
	n	(%)	n	(%)	n	(%)
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)
Bath Ankylosing Spondylitis Disease activity Index (BASDAI)						
Less than or Equal to Median (63.5)	44	(44.9)	55	(55.0)	99	(50.0)
Greater than Median (63.5)	54	(55.1)	45	(45.0)	99	(50.0)
Disease Durations Category (Yrs)						
<1	67	(68.4)	65	(65.0)	132	(66.7)
1-2	20	(20.4)	19	(19.0)	39	(19.7)
3-5	11	(11.2)	16	(16.0)	27	(13.6)
Disease Duration Range (Yrs)						
Less than or Equal to Median (0.5)	50	(51.0)	49	(49.0)	99	(50.0)
Greater than Median (0.5)	48	(49.0)	51	(51.0)	99	(50.0)
Number of Failed Prior NSAIDS						
0	14	(14.3)	8	(8.0)	22	(11.1)
1	30	(30.6)	38	(38.0)	68	(34.3)
2	35	(35.7)	38	(38.0)	73	(36.9)
>2	19	(19.4)	16	(16.0)	35	(17.7)
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	
Chest Wall Expansion (cm)						

Table 4: Summary of Demographic and Disease Characteristics All Randomized Subjects			
	GLM 50mg n (%)	Placebo n (%)	Total n (%)
Subjects with data	94	97	191
Mean	5.25	4.76	5.00
SD	2.217	2.063	2.149
Median	5.00	5.00	5.00
Range	1.0 to 12.0	1.0 to 11.0	1.0 to 12.0
Patient Global Disease Assessment VAS (cm)			
Subjects with data	97	100	197
Mean	6.93	6.31	6.62
SD	1.926	2.220	2.098
Median	7.30	6.60	7.10
Range	0.6 to 9.8	0.1 to 10.0	0.1 to 10.0
Total Back Pain VAS (cm)			
Subjects with data	97	100	197
Mean	6.96	6.67	6.81
SD	1.765	1.694	1.731
Median	7.10	6.55	6.90
Range	1.2 to 9.9	3.6 to 10.0	1.2 to 10.0
Nocturnal Back Pain VAS (cm)			
Subjects with data	97	100	197
Mean	7.10	6.38	6.73
SD	2.188	2.427	2.335
Median	7.50	6.75	7.20
Range	0.4 to 10.0	0.5 to 10.0	0.4 to 10.0
BASDAI Score (cm)			
Subjects with data	97	100	197
Mean	6.609	6.369	6.487
SD	1.5619	1.4873	1.5254
Median	6.660	6.240	6.350
Range	3.49 to 9.95	3.45 to 9.67	3.45 to 9.95
ASDAS-C Score			
Subjects with data	97	100	197
Mean	3.6	3.5	3.5
SD	0.9	0.8	0.9
Median	3.5	3.4	3.5
Range	1.5 to 6.4	2.0 to 5.3	1.5 to 6.4
BASFI Score (cm)			
Subjects with data	97	100	197
Mean	5.264	4.769	5.013
SD	2.3593	2.5318	2.4547
Median	5.230	5.005	5.170
Range	0.42 to 10.00	0.12 to 9.90	0.12 to 10.00
BASMI Score (cm)			
Subjects with data	97	100	197
Mean	2.41	2.51	2.46

Table 4: Summary of Demographic and Disease Characteristics All Randomized Subjects			
	GLM 50mg n (%)	Placebo n (%)	Total n (%)
SD	1.303	1.322	1.310
Median	2.20	2.20	2.20
Range	0.2 to 7.4	0.4 to 5.6	0.2 to 7.4
MASES Score			
Subjects with data	95	98	193
Mean	3.1	3.3	3.2
SD	3.4	3.4	3.4
Median	2.0	2.0	2.0
Range	0.0 to 13.0	0.0 to 13.0	0.0 to 13.0
SPARCC MRI SI Joint 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
Swollen Joint Count 44			
Subjects with data	97	100	197
Mean	1.5	1.5	1.5
SD	2.5	2.9	2.7
Median	0.0	0.0	0.0
Range	0.0 to 10.0	0.0 to 15.0	0.0 to 15.0
Tender Joint Count 44			
Subjects with data	97	100	197
Mean	3.9	3.2	3.5
SD	5.9	5.7	5.8
Median	1.0	1.0	1.0
Range	0.0 to 30.0	0.0 to 35.0	0.0 to 35.0

[1]subject who is reported as being 46 years old was actually 45 years old at the time of screening.

Demographic and subject characteristics and most baseline disease characteristics in the OSI population were similar between the treatment groups and generally similar to those of the overall population. As expected, there were differences between the overall and OSI populations in terms of baseline MRI SI Joint scores and CRP levels, given the definition of the OSI population. Mean Baseline SPARCC MRI SI Joint levels were 11.3 vs. 14.1 in the overall and OSI populations, respectively, and mean Baseline CRP scores were 1.40 mg/dL vs. 1.68 mg/dL in the overall and OSI populations, respectively.

Numbers analysed

Part 1 efficacy data were evaluated separately from those of Part 2. At the time of Stage 1 lock, all subjects had completed Week 24. Efficacy analyses were performed using the FAS, Per Protocol, and OSI populations. Safety analyses were performed using the ASaT population. Part 1 safety data were evaluated separately from those of Part 2. In addition, cumulative exposure-adjusted AE incidence was provided from randomization to the end of the trial to evaluate the longer term (60 weeks) safety profile. Some subjects were ongoing in Part 2 and their data were analysed up to May 6, 2014 when the final subject completed their Week 24 visit.

Outcomes and estimation

Primary endpoint analysis

The primary endpoint, ASAS 20 response at Week 16, was analysed using the FAS population, consisting of all randomized subjects who received at least 1 dose of study treatment in Part 1 (n=197).

The primary objective was achieved. A significantly greater proportion of subjects in the golimumab 50 mg group achieved ASAS 20 response compared with subjects in the placebo group (71.1% vs 40.0% in the golimumab 50 mg and placebo groups respectively, p<0.0001; Table 5).

Table 5 Primary Endpoint: Analysis of the Proportion of Subjects Achieving ASAS 20 Response at Week 16 in Study P07642 -- Full Analysis Set Population

	Responder		Difference in % vs Placebo	
Treatment	n/N	%	Estimate (95% CI)‡	P-value‡
GLM 50 mg	69 /97	71.1	31.2 (17.5, 43.6)	<0.0001
Placebo	40 /100	40.0		

‡ 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.

No subjects met the treatment failure criteria prior to Week 16; however, 7 subjects were analysed as non-responders because they discontinued prior to Week 16: 4 (2%) in the golimumab 50 mg group and 3 (1.5%) in the placebo group.

The treatment effects of golimumab 50 mg versus placebo across most of the subgroups based on demographics and baseline disease characteristics were consistent with the treatment effect observed in the FAS population. In the subgroup analysis based on stratification factors, no treatment benefit was observed for subjects with the combination of negative MRI and CRP within normal limits at baseline.

Sensitivity Analyses

To test the robustness of the primary analysis, a sensitivity analyses in which subjects who discontinued due to an AE were considered non-responders was performed. The results are identical to those based on the primary approach since in both approaches subjects who discontinued prior to Week 16 were considered non-responders.

Per protocol analyses

The per protocol population excluded 23 subjects based on a set of pre-specified criteria, 13 from the golimumab 50 mg group and 10 from the placebo group. The subjects who met pre-specified criteria included 8 (4%) with violations on the exclusion and inclusion criteria, 9 (4.5%) with low medication compliance or early discontinuation from Part I (since these subjects did not receive all 4 doses of study medication), 4 (2%) for use of prohibited medications or unstable NSAID use (i.e. change in dose, initiation of a new NSAID or discontinuation of NSAID) during Part 1 and 3 (2%) with a large visit window between visits. One subject was counted in two criteria.

Table 6: Analysis of the Proportion of Subjects Achieving ASAS 20 Response at Week 16 Per Protocol Population (Part 1)

	Responder		Difference in % vs Placebo	
Treatment	n/N	%	Estimate (95% CI)‡	P-value‡
GLM 50 mg	63 /84	75.0	36.4 (22.0, 49.2)	<0.0001
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.

Key Secondary Endpoints

Table 7: Analysis of the Proportion of Subjects Achieving ASAS 40 Response at Week 16 Full-Analysis-Set Population (Part 1)

	Responder		Difference in % vs Placebo	
Treatment	n/N	%	Estimate (95% CI)‡	P-value‡
GLM 50 mg	55 /97	56.7	33.8 (20.4, 46.1)	<0.0001
Placebo	23 /100	23.0		

‡ 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 8: Analysis of the Proportion of Subjects Achieving BASDAI50 at Week 16 Full-Analysis-Set Population (Part 1)

	Responder		Difference in % vs Placebo	
Treatment	n/N	%	Estimate (95% CI)‡	P-value‡
GLM 50 mg	56 /97	57.7	28.0 (14.4, 40.6)	<0.0001
Placebo	30 /100	30.0		

‡ 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 9: Analysis of the Proportion of Subjects Achieving ASAS Partial Remission at Week 16 Full-Analysis-Set Population (Part 1)

	Responder		Difference in % vs Placebo	
Treatment	n/N	%	Estimate (95% CI)‡	P-value‡
GLM 50 mg	32 /97	33.0	15.2 (3.2, 27.1)	0.0136
Placebo	18 /100	18.0		

‡ 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 10: Analysis of Change from Baseline in SPARCC MRI SI Joints at Week 16 (Primary approach) Subjects who Completed Part 1 from Full Analysis Set

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

Other secondary endpoints

Table 11: Other Secondary Endpoints at Week 16 Full Analysis Set Population

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
BASFI (cm)							
GLM 50mg	93	5.264 (2.3762)	2.502 (2.5340)	-2.632 (0.2251)	(-3.076 to -2.188)	-1.728 (-2.330, -1.125)	<0.0001
Placebo	97	4.695 (2.5302)	3.873 (2.8265)	-0.905 (0.2205)	(-1.339 to -0.470)		
BASMI (cm)							
GLM 50mg	94	2.40 (1.292)	1.93 (1.182)	-0.48 (0.071)	(-0.62 to -0.34)	-0.39 (-0.58, -0.20)	<0.0001
Placebo	100	2.51 (1.322)	2.42 (1.387)	-0.08 (0.068)	(-0.22 to 0.05)		
C-Reactive Protein (mg/dL)							
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)		
ASDAS-C Score							
GLM 50mg	88	3.590 (0.9383)	1.869 (1.0161)	-1.685 (0.1187)	(-1.919 to -1.451)	-1.053 (-1.373, -0.733)	<0.0001
Placebo	90	3.403 (0.7861)	2.803 (1.2178)	-0.631 (0.1167)	(-0.861 to -0.401)		
SF-36 Mental Component Summary Score							
GLM 50mg	91	41.10 (11.940)	47.06 (11.084)	5.85 (1.113)	(3.66 to 8.05)	4.24 (1.42, 7.07)	0.0034
Placebo	96	41.55 (11.135)	43.08 (11.840)	1.61 (1.086)	(-0.53 to 3.75)		
SF-36 Physical Component Summary Score							
GLM 50mg	91	32.85 (8.083)	43.43 (10.211)	10.29 (0.847)	(8.62 to 11.96)	6.56 (4.28, 8.83)	<0.0001
Placebo	96	34.97 (8.682)	38.33 (9.649)	3.74 (0.824)	(2.11 to 5.36)		
ASQoL Score							
GLM 50mg	94	11.1 (4.45)	5.6 (5.16)	-5.2 (0.48)	(-6.2 to -4.3)	-3.5 (-4.7, -2.2)	<0.0001
Placebo	100	10.2 (4.57)	8.6 (5.09)	-1.8 (0.47)	(-2.7 to -0.9)		
Swollen Joint Count Score							
GLM 50mg	93	1.4 (2.49)	0.7 (2.81)	-0.8 (0.22)	(-1.2 to -0.4)	-0.3 (-0.9, 0.3)	0.2825
Placebo	100	1.5 (2.92)	1.0 (2.39)	-0.5 (0.21)	(-0.9 to -0.1)		

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
Tender Joint Count Score							
GLM 50mg	93	3.9 (5.83)	2.3 (6.53)	-1.4 (0.46)	(-2.3 to -0.5)	-0.8 (-2.1, 0.4)	0.1887
Placebo	100	3.2 (5.67)	2.7 (5.50)	-0.6 (0.44)	(-1.5 to 0.3)		
Chest Wall Expansion (cm)							
GLM 50mg	90	5.31 (2.240)	5.60 (2.203)	0.33 (0.155)	(0.02 to 0.63)	0.31 (-0.10, 0.72)	0.1406
Placebo	97	4.76 (2.063)	4.79 (1.917)	0.02 (0.150)	(-0.28 to 0.31)		
EQ-5D Health State Score (cm)							
GLM 50mg	94	4.47 (2.193)	6.75 (2.378)	2.09 (0.235)	(1.63 to 2.55)	1.51 (0.91, 2.12)	<0.0001
Placebo	100	5.10 (2.066)	5.53 (2.349)	0.57 (0.228)	(0.12 to 1.02)		
Patient's Global Disease Assessment (cm)							
GLM 50mg	93	6.96 (1.940)	2.98 (2.911)	-3.70 (0.319)	(-4.33 to -3.07)	-2.21 (-3.05, -1.38)	<0.0001
Placebo	96	6.23 (2.220)	4.97 (3.182)	-1.49 (0.314)	(-2.10 to -0.87)		
BASDAI Inflammation Score (cm)							
GLM 50mg	93	6.802 (1.8856)	2.844 (2.4769)	-3.816 (0.2459)	(-4.301 to -3.331)	-2.011 (-2.675, -1.347)	<0.0001
Placebo	96	6.098 (2.0548)	4.394 (2.7956)	-1.805 (0.2413)	(-2.281 to -1.329)		
Total Back Pain (cm)							
GLM 50mg	93	6.98 (1.775)	2.77 (2.783)	-4.09 (0.300)	(-4.68 to -3.50)	-2.13 (-2.94, -1.32)	<0.0001
Placebo	97	6.61 (1.674)	4.74 (3.170)	-1.96 (0.294)	(-2.54 to -1.38)		
Nocturnal Pain (cm)							
GLM 50mg	93	7.13 (2.201)	2.51 (2.697)	-4.37 (0.300)	(-4.96 to -3.78)	-2.63 (-3.42, -1.84)	<0.0001
Placebo	97	6.30 (2.422)	4.78 (3.259)	-1.74 (0.294)	(-2.32 to -1.16)		
Physicians Global Disease Assessment (cm)							
GLM 50mg	93	6.20 (1.870)	2.22 (2.194)	-4.03 (0.255)	(-4.53 to -3.53)	-1.75 (-2.41, -1.08)	<0.0001
Placebo	100	6.33 (1.634)	4.02 (2.608)	-2.29 (0.247)	(-2.77 to -1.80)		

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
MASES Index Score							
GLM 50mg	92	3.2 (3.36)	1.7 (2.95)	-1.4 (0.26)	(-1.9 to -0.9)	-0.7 (-1.4, -0.1)	0.0302
Placebo	97	3.2 (3.35)	2.5 (3.18)	-0.7 (0.25)	(-1.2 to -0.2)		

†Derived using a constrained longitudinal data analysis (cLDA) model including 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.

Table 12: Other Secondary Endpoints at Week 16 Full Analysis Set Population ASAS 5/6, ADAS-C Inactive Disease/clinical remission

Treatment	Responder n/N	%	Difference in % vs Placebo Estimate (95% CI)‡	P-value‡
ASAS 5/6				
GLM 50 mg	52 /97	53.6	30.7 (17.7, 43.0)	<0.0001
Placebo	23 /100	23.0		
ASDAS-C Inactive Disease/clinical remission (< 1.3)				
GLM 50 mg	29 /88	33.0	19.8 (7.7, 32.0)	0.0016
Placebo	12 /90	13.3		

‡ 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 13: Work Productivity and Activity Impairment (WPAI) at Week 16 Full Analysis Set Population

Treatment	N	Baseline		Week 16	Change From Baseline at Week 16	Difference vs Placebo†	
		Mean	Median	Mean (SD)	Mean (SD)	Score	p-value
Number Currently Employed							
GLM 50mg	72						
Placebo	69						
Percent Work Time Missed Due to Health							
GLM 50mg	58	11.3	0.0	5.5 (20.57)	-5.8 (16.28)	-1.6	0.1103
Placebo	58	13.4	0.0	14.3 (25.21)	0.9 (27.89)		
Percent Impairment While Working Due to Health							
GLM 50mg	63	43.7	40.0	21.3 (22.82)	-22.4 (25.76)	1.9	0.0525
Placebo	58	49.3	50.0	35.3 (28.17)	-14.0 (28.71)		
Percent Overall Work Impairment Due to Health							
GLM 50mg	57	43.0	40.0	22.0 (23.90)	-21.1 (24.68)	-2.1	0.0391
Placebo	57	53.2	53.9	41.5 (30.93)	-11.7 (28.21)		
Percent Activity Impairment Due to Health							
GLM 50mg	93	55.1	60.0	30.1 (27.88)	-24.9 (29.51)	-3.9	<0.0001
Placebo	100	54.4	60.0	45.8 (29.20)	-8.6 (27.63)		

† Derived based on Mann-Whitney Test.
Includes subjects with WPAI scores at Baseline and Week 16

Efficacy at Week 24

At Week 16, subjects on placebo switched to open-label golimumab 50 mg Q4W. In this study, 190 subjects completed Part 1 and 187 subjects completed through Week 24.

Of the 69 golimumab 50 mg/golimumab 50 mg subjects who achieved **ASAS 20** response at Week 16, 66 (95.7%) achieved ASAS 20 response at Week 24. Twelve of 24 (50.0%) subjects who did not have an ASAS 20 response at Week 16 were responders at Week 24

Table 14: Summary of Proportion of Subjects Achieving ASAS 20 at Week 24 by Week 16 Responder Status Full-Analysis-Set Population

	ASAS20 Responders		
	Week 16 Responder Status n/N (%)		Total n/N (%)
	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)

Of the 55 golimumab 50 mg/golimumab 50 mg subjects who achieved **ASAS 40** response at Week 16, 51 (92.7%) were responders at Week 24. Seventeen of 38 (44.7%) subjects who did not have an ASAS 40 response at Week 16 were responders at Week 24

Of the 56 golimumab 50 mg/golimumab 50 mg subjects who achieved **BASDAI 50** response at Week 16, 51 (91.1%) achieved BASDAI 50 response at Week 24. Nineteen of 37 (51.4%) subjects who did not have a BASDAI 50 response at Week 16, were responders at Week 24.

Of the 32 golimumab 50 mg/golimumab 50 mg subjects who achieved **ASAS partial remission** response at Week 16, 29 (90.6%) achieved ASAS partial remission response at Week 24. Ten of 61 (16.4%) subjects who did not have an ASAS partial remission response at Week 16 were responders at Week 24.

Table 15: Summary of Proportion of Subjects Achieving ASAS 40, BASDAI 50 and ASAS Partial Remission at Week 24 by Week 16 Responder Status Full-Analysis-Set Population

	Week 16 Responder Status n/N (%)		Total n/N (%)
	Responder	Non-responder	
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)

Overall, the proportion of subjects with an **ASAS 20** response in the group randomized to golimumab 50 mg increased from 71.1% at Week 16 to 83.9% at Week 24. The proportion of subjects with **ASAS 40** response in the golimumab group increased from 56.7% at Week 16 to 73.1%, and **BASDAI 50** response increased from 57.7% at Week 16 to 75.3% at Weeks 24.The proportion of subjects with **ASAS partial remission** response in the golimumab group increased from 33.0% at Week 16 to and 41.9% at Week 24. The proportion of subjects with **ASDAS-C Inactive disease/ clinical remission (<1.3)** increased from 33.0% at Week 16 to 40.9% at Week 24 in the golimumab group.

Table 16: Summary of Proportion of Subjects at Week 16 and Week 24 Full Analysis Set Population

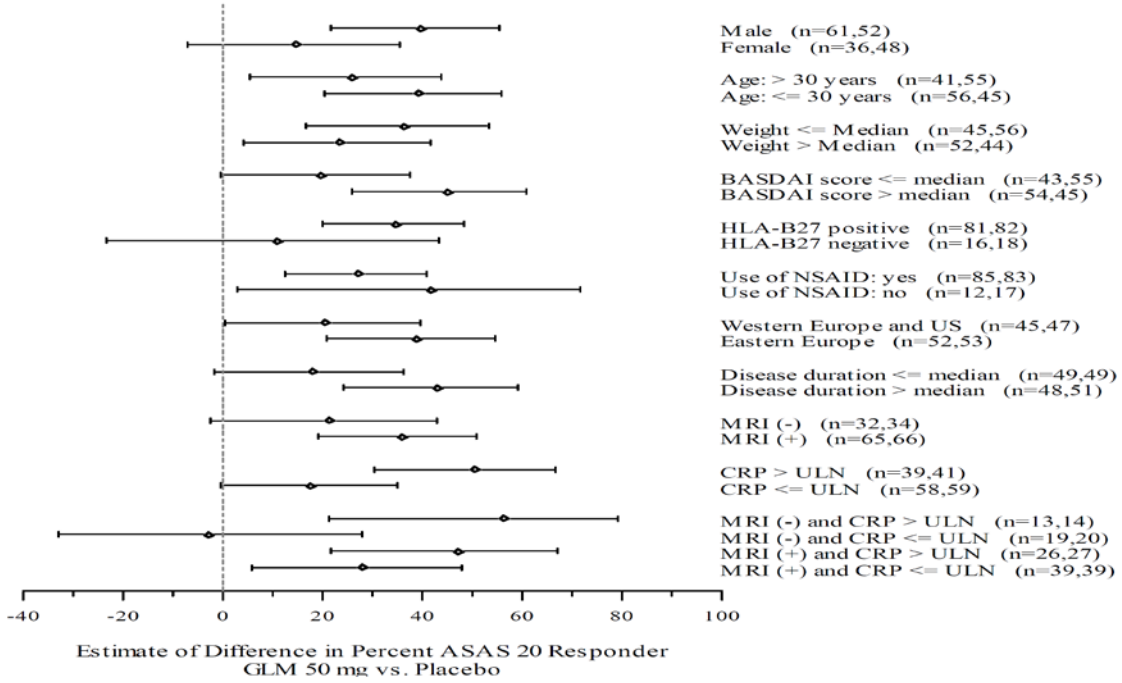
Endpoint Treatment Group	Week 16 n/N (%)	Week 24 n/N (%)
ASAS 20		
GLM 50 mg/GLM 50 mg	69 /97 (71.1)	78/ 93 (83.9)
Placebo/GLM 50 mg	40 /100 (40.0)	68/ 96 (70.8)
ASAS 40		
GLM 50 mg/GLM 50 mg	55 /97 (56.7)	68/ 93 (73.1)
Placebo/GLM 50 mg	23 /100 (23.0)	50/ 96 (52.1)
BASDAI 50		
GLM 50 mg/GLM 50 mg	56 /97 (57.7)	70/ 93 (75.3)
Placebo/GLM 50 mg	30 /100 (30.0)	55/ 96 (57.3)
ASAS partial remission	32 /97 (33.0)	39/ 93 (41.9)
GLM 50 mg/GLM 50 mg	18 /100 (18.0)	41/ 96 (42.7)
Placebo/GLM 50 mg		
ASAS 5/6	52 /97 (53.6)	56/ 93 (60.2)
GLM 50 mg/GLM 50 mg	23 /100 (23.0)	45/ 96 (46.9
Placebo/GLM 50 mg		
ASDAS-C Inactive disease/clinical remission (<1.3)	29 /88 (33.0)	36/ 88 (40.9)
GLM 50 mg/GLM 50 mg	12 /90 (13.3)	40/ 89 (44.9)
Placebo/GLM 50 mg		

Ancillary analyses

Four (4.3%) subjects developed antibodies to golimumab 50 mg through Week 16. All 4 subjects achieved ASAS20 at Week 16. This suggests that development of immunogenic response had little impact on efficacy.

Treatment comparisons for pre-specified subgroups defined by demographic, baseline characteristics and stratification factors on ASAS 20 and ASAS 40 responder rates were performed. These included: gender, age (>30 yrs and <=30yrs), weight (<=median, 76 kg, >median, 76 kg), BASDAI score (<=median, 6.35 cm >median, 6.35 cm), HLA-B27 status, use of NSAIDS, region (Western Europe and US, Eastern Europe), MRI (positive, negative) and CRP status (≤ULN, >ULN [0.9 mg/dL]). Differences between treatment groups, along with 95% CIs and p-values were calculated. No multiplicity control was applied to these statistical tests; results must be interpreted with caution.

Figure 3: Difference in Percent ASAS 20 Responder Status at Week 16 by Baseline Factors Point Estimate and 95% Confidence Interval GLM 50mg versus Placebo Full-Analysis-Set Population (Part 1)



ASAS 20 responses favouring golimumab 50 mg over placebo were observed in most subgroups with the exception of subjects with the combination of negative MRI and CRP within normal limits at baseline. For this subgroup, no difference in the ASAS 20 response rate between golimumab 50 mg and placebo was seen. ASAS 40 responses favouring golimumab 50 mg over placebo were observed in all subgroups.

OSI Population

The OSI population consisted of 158 subjects (80 % of all treated subjects).

The proportions of subjects in the OSI population who achieved ASAS 20, ASAS40, BASDAI 50 and ASAS Partial Remission at Week 16 are presented in Table 17. The proportion of responders was significantly greater in the golimumab 50 mg group than in the placebo group for all of these measures ($p<0.0001$ for ASAS 20, ASAS 40, BASDAI 50; $p=0.0204$ for ASAS partial remission).

The SPARCC MRI SI joints score had significantly greater reduction from baseline in the golimumab 50 mg group than in the placebo group at Week 16 ($p<0.0001$).

Other secondary endpoints were analyzed for the OSI population at Week 16. For all these endpoints, a significant treatment benefit was observed for subjects in the OSI population treated with golimumab 50 mg versus placebo.

The magnitude of effect with golimumab in the OSI population was numerically similar to or greater than what was observed in the overall study population

Table 17: ASAS20, ASAS40, BASDAI 50 and ASAS Partial Remission at Week 16 OSI Population

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.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial P07642

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study of the Effect of Golimumab (GLM) Administered Subcutaneously (SC) in Subjects with Active Axial Spondyloarthritis (SpA) (Phase 3b, Protocol No. P07642, also known as MK-8259-006-02, and as GO-AHEAD).			
Study identifier	P07642		
Design	Double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks Not Applicable Not Applicable
Hypothesis	Superiority		
Treatments groups	GLM		Golimumab 50 mg SC at Baseline, at Weeks 4, 8, and 12 number randomized: 98 (only 97 subjects received treatment)
	PBO		Placebo SC at Baseline, at Weeks 4, 8, and 12 number randomized: 100
Endpoints and definitions	Primary endpoint	ASAS 20	% of subjects who achieve ≥20% improvement in the Assessment of SpondyloArthritis international Society (ASAS 20)
	Key Secondary endpoint	ASAS 40	% of subjects who achieve ≥40% improvement in ASAS (ASAS 40)
	Key Secondary endpoint	BASDAI 50	% of subjects who achieve ≥50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50)
	Key Secondary endpoint	ASAS Partial Remission	% of subjects who achieve Partial Remission in ASAS
	Key Secondary endpoint	MRI SI-joint SPARCC score	Change from baseline in score for sacroiliac-joint inflammation on magnetic resonance imaging using SPondyloArthritis Research Consortium of Canada (SPARCC) score
	Secondary endpoint	Total Back Pain	Change from baseline in total back pain
	Secondary endpoint	BASDAI Inflammation	Change from baseline in overall morning stiffness

	Secondary endpoint	BASFI	Improvement in physical function as assessed by BASFI
	Secondary endpoint	PGDA	Change from baseline in Patient's Global Disease Assessment
	Secondary endpoint	ASAS 5/6	% of subjects who achieve a 20% improvement in any 5 of the 6 domains of pain, patient global function (BASFI score), morning stiffness, CRP, and spine mobility
	Secondary endpoint	BASMI	Improvement in hip and spinal mobility
	Secondary endpoint	CRP	Change from baseline in C-Reactive Protein
	Secondary endpoint	ASDAS-C Score	Change from baseline in disease activity score
	Secondary endpoint	ASDAS-C (<1.3)	% of subjects who achieve ASDAS inactive disease (ASDAS-C <1.3)
	Secondary endpoints	Health-related Quality of Life	Improvement in health-related quality of life as assessed by SF-36 physical component summary (PCS) and mental component summary (MCS) scores, ASQoL, and EQ-5D.
Database lock	26 May 2014		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Population: Full Analysis Set (all randomized subjects who received at least one dose of study treatment) at Week 16 – NRI, LOCF, and Observed cases. Time point: Week 16

Descriptive statistics and estimate variability

Treatment group	**GLM**			**PBO**		
	N	Responders (%)		N	Responders (%)	
ASAS 20	97	71.1		100	40.0	
ASAS 40	97	56.7		100	23.0	
BASDAI 50	97	57.7		100	30.0	
ASAS Partial Remission	97	33.0		100	18.0	
	N	Mean	Standard Deviation	N	Mean	Standard Deviation
SPARCC MRI SI Joint Score	74	4.6	7.92	87	11.7	14.79
Total Back Pain (cm)	93	-4.2	2.94	97	-1.9	3.02
BASDAI Inflammation (cm)	93	-4.0	2.42	96	-1.7	2.50
BASFI (cm)	93	-2.8	2.45	97	-0.8	2.08
PGDA (cm)	93	-4.0	3.22	96	-1.3	3.32
	N	Responders (%)		N	Responders (%)	
ASAS 5/6	97	53.6		100	23.0	
	N	Mean	Standard Deviation	N	Mean	Standard Deviation
BASMI (cm)	94	-0.5	0.79	100	-0.1	0.60
CRP (mg/dL)	88	-1.1	2.66	91	-0.3	1.72
ASDAS-C Score	88	-1.7	1.30	90	-0.6	1.06

		Responders N	Responders (%)		Responders N	Responders (%)	
	ASDAS-C (<1.3)	88	33		90	13.3	
		N	Mean	Standard Deviation	N	Mean	Standard Deviation
	SF-36 MCS Score	91	6.0	11.46	96	1.5	11.53
	SF-36 PCS Score	91	10.6	9.70	96	3.4	6.82
	ASQoL Score	94	-5.4	5.57	100	-1.6	4.08
	EQ-5D Health State VAS (cm)	94	2.3	2.78	100	0.4	2.00
Effect estimate per comparison	Primary endpoint: ASAS 20	Comparison groups			GLM vs PBO		
		Difference in %			31.2 ‡		
		95% CI			(17.5, 43.6) ‡		
		P-value			<0.0001‡		
	Key Secondary endpoint: ASAS 40	Comparison groups			GLM vs PBO		
		Difference in %			33.8 ‡		
		95% CI			(20.4, 46.1) ‡		
		P-value			<0.0001‡		
	Key Secondary endpoint: BASDAI 50	Comparison groups			GLM vs PBO		
		Difference in %			28.0 ‡		
		95% CI			(14.4, 40.6) ‡		
		P-value			<0.0001‡		
	Key Secondary endpoint: ASAS Partial Remission	Comparison groups			GLM vs PBO		
		Difference in %			15.2 ‡		
		95% CI			(3.2, 27.1) ‡		
		P-value			0.0136‡		
	Key Secondary endpoint: MRI SI-joint SPARCC score	Comparison Groups			GLM vs PBO		
		Score statistic			-4.3 *		
		P-value			<0.0001*		
	Secondary endpoint: Total Back Pain	Comparison groups			GLM vs PBO		
		Adjusted difference in means			-2.1 †		
		95% CI			(-2.94, -1.32) †		
		P-value			<0.0001†		
	Secondary endpoint: BASDAI Inflammation	Comparison groups			GLM vs PBO		
		Adjusted difference in means			-2.0 †		
		95% CI			(-2.68, -1.35) †		
		P-value			<0.0001†		
	Secondary endpoint: BASFI	Comparison groups			GLM vs PBO		
		Adjusted difference in means			-1.7 †		
		95% CI			(-2.33, -1.13) †		
		P-value			<0.0001†		
	Secondary endpoint: PGDA	Comparison groups			GLM vs PBO		
		Adjusted difference in means			-2.2 †		
		95% CI			(-3.05, -1.38) †		
		P-value			<0.0001†		
	Secondary endpoint: ASAS 5/6	Comparison groups			GLM vs PBO		
		Difference in %			30.7 ‡		
		95% CI			(17.7, 43.0) ‡		
		P-value			<0.0001‡		
	Secondary endpoint: BASMI	Comparison groups			GLM vs PBO		
		Adjusted difference in means			-0.4 †		
		95% CI			(-0.58, -0.20) †		
		P-value			<0.0001†		

	Secondary endpoint: CRP	Comparison groups	GLM vs PBO
		Adjusted difference in means	-0.6 †
		95% CI	(-0.98, -0.30) †
		P-value	0.0003†
	Secondary endpoint: ASDAS-C Score	Comparison groups	GLM vs PBO
		Adjusted difference in means	-1.1 †
		95% CI	(-1.37, -0.73) †
		P-value	<0.0001†
	Secondary endpoint: ASDAS-C (<1.3)	Comparison groups	GLM vs PBO
		Difference in %	19.8 ‡
		95% CI	(7.7, 32.0) ‡
		P-value	0.0016 ‡
	Secondary endpoint: SF-36 MCS Score	Comparison groups	GLM vs PBO
		Adjusted difference in means	4.2 †
		95% CI	(1.42, 7.07) †
		P-value	0.0034†
	Secondary endpoint: SF-36 PCS Score	Comparison groups	GLM vs PBO
		Adjusted difference in means	6.6 †
		95% CI	(4.28, 8.83) †
		P-value	<0.0001†
	Secondary endpoint: ASQoL Score	Comparison groups	GLM vs PBO
		Adjusted difference in means	-3.5 †
		95% CI	(-4.7, -2.2) †
		P-value	<0.0001†
	Secondary endpoint: EQ-5D Health State	Comparison groups	GLM vs PBO
		Adjusted difference in means	1.5 †
		95% CI	(0.91, 2.12) †
		P-value	<0.0001†

Analysis description	**Pre-specified subpopulation analysis**
Analysis population and time point description	Population: FAS subjects with Objective signs of inflammation (subjects with Baseline evidence of sacroiliitis on MRI and/or screening CRP level > upper level of normal) – NRI, LOCF, and Observed cases. Time point: Week 16

Descriptive statistics and estimate variability	**Treatment group**	**GLM**			**PBO**		
		N	Responders (%)		N	Responders (%)	
	ASAS 20	78	76.9		80	37.5	
	ASAS 40	78	60.3		80	22.5	
	BASDAI 50	78	59.0		80	28.8	
	ASAS Partial Remission	78	34.6		80	18.8	
		N	Mean	Standard Deviation	N	Mean	Standard Deviation
	SPARCC MRI SI Joint score	61	-6.4	8.07	69	-1.2	9.58
	Total Back Pain (cm)	76	-4.4	2.93	78	-1.8	3.03
	BASDAI Inflammation (cm)	76	-4.1	2.44	77	-1.6	2.41
	BASFI (cm)	76	-2.9	2.42	78	-0.8	2.16
	PGDA (cm)	76	-4.2	3.28	77	-1.1	3.46
Effect	Primary	Comparison groups			GLM vs PBO		

estimate per comparison	endpoint: ASAS 20	Difference in %	39.6 ‡
		95% CI	(24.6, 52.6) ‡
		P-value	<0.0001‡
	Key Secondary endpoint: ASAS 40	Comparison groups	GLM vs PBO
		Difference in %	37.9 ‡
		95% CI	(23.0, 51.2) ‡
		P-value	<0.0001‡
	Key Secondary endpoint: BASDAI 50	Comparison groups	GLM vs PBO
		Difference in %	30.5 ‡
		95% CI	(15.4, 44.3) ‡
		P-value	<0.0001‡
	Key Secondary endpoint: ASAS Partial Remission	Comparison groups	GLM vs PBO
		Difference in %	16.1 ‡
		95% CI	(2.5, 29.6) ‡
		P-value	0.0204‡
	Key Secondary endpoint: MRI SI-joint SPARCC score	Comparison groups	GLM vs PBO
		Score statistic	-3.9 *
		P-value	<0.0001*
	Secondary endpoint: Total Back Pain	Comparison groups	GLM vs PBO
		Adjusted difference in means	-2.4 †
		95% CI	(-3.29, -1.46) †
		P-value	<0.0001†
	Secondary endpoint: BASDAI Inflammation	Comparison groups	GLM vs PBO
		Adjusted difference in means	-2.3 †
		95% CI	(-3.02, -1.54) †
		P-value	<0.0001†
	Secondary endpoint: BASFI	Comparison groups	GLM vs PBO
		Adjusted difference in means	-1.9 †
		95% CI	(-2.58, -1.22) †
		P-value	<0.0001†
	Secondary endpoint: PGDA	Comparison groups	GLM vs PBO
		Adjusted difference in means	-2.4 †
		95% CI	(-3.38, -1.46) †
		P-value	<0.0001†
Notes	‡ *P* value for categorical variables (NRI imputation for missing values) was based on stratified Miettenen & Nurminen test. * *P* value for MRI SPARCC score (as observed) was based on Mann Whitney statistic. † *P* value for continuous variables (as observed) was based on cLDA adjusting for stratification factors and treatment. N: Number of subjects NRI (non-responder imputation): missing response was imputed as non-response. LOCF (last observation carried forward): missing response was imputed with last non-missing value.		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The proposed posology for Simponi is 50 mg given subcutaneously once a month. For patients weighing >100 kg the dose should be 100 mg. This is in line with the posology of the already approved AS-indication, and is endorsed.

The MAH has submitted one pivotal study, P07642. In total, 198 subjects, whereof 125 subjects from EU representing 63% of all subjects, 63 subjects from Russia, and Turkey (32%) and 10 from US (5%) were randomized.

The included subjects were to have a diagnosis of active Axial SpA showing no evidence of radiographically (x-ray) defined sacroiliitis with chronic back pain ≥3 months, and an inadequate response or intolerance to therapy with NSAIDs.

Subjects were stratified based on whether they had active inflammation on MRI of the sacroiliac joint (yes/no) and CRP level (≤upper limit of normal/ >upper limit of normal). Subjects without evidence of sacroiliitis on MRI (using a central reader) were limited to 50% of the total enrolled population. Subjects with a normal CRP level at screening (according to the central lab) were limited to 60% of total enrolled. Treated subjects with baseline evidence of sacroiliitis on MRI and/or screening C-reactive protein (CRP) level >upper limit of normal (ULN; 0.9 mg/dL) made up the prespecified Objective signs of inflammation OSI population.

The primary endpoint was ASAS20 response at Week 16. Key secondary endpoints were ASAS40, BASDAI50, ASAS partial remission and change from baseline in the SPARCC RI SI joint score.

The design of the study is generally endorsed. The chosen primary endpoint is acceptable; however, ASAS40 is of greater interest, since this result is a realistic goal using the products currently on the market. Since this is a key secondary endpoint, the study design is acceptable.

During the study, 8 sites reported having visual analogue scales that were not the standard 100 mm length. Twelve patents were affected, whereof 2 were randomized. A full investigation was conducted, a mathematical conversion of the results was made and corrected scales provided. This is acceptable.

The MAH pointed out that it was possible that a subject had a good response initially to NSAIDs, however, subsequently had inadequate response for 30 days or developed intolerance to NSAID therapy. This is reasonable to CHMP, and this inclusion criterion may be compatible with meeting the NSAID good response criterion for the diagnosis.

It is noted that there seems to be a difference between males and females in achieving the primary endpoint as compared to placebo. This is seen also for ASAS40. The finding is noteworthy, since there was an imbalance between groups, with fewer females in the golimumab group. A similar outcome pattern has occurred with the age groups ≤30 and >30. The MAH has provided a weighted response analysis, showing that the gender and age imbalance between treatment groups did not have a substantial impact on the overall results. The overall size of the result is thus not considered to have been driven by the imbalance and potential effect difference in sex and age.

Efficacy data and additional analyses

The primary endpoints were met. The difference in the percentage of subjects that achieved ASAS 20 response at Week 16 between the groups was 31.2% (71.1% vs 40.0% in the golimumab 50 mg and placebo groups respectively, p<0.0001). The primary endpoint analysis was also robust to the exclusion of subjects with pre-specified protocol deviations and to considering subjects who discontinued due to an adverse event as non-responders; the results for both the Per-protocol and sensitivity analyses were consistent with that based on the primary approach. The number of patients discontinuing prior to Week 16 are evenly distributed for the two treatments, which is reassuring for the robustness of the primary results. However there was no information available in the study report about the amount of missing data on the component-wise level for patients remaining in study. Based on the data provided by the MAH the CHMP concluded that the impact of missing data on the evaluation results is small.

All key secondary endpoints were met, the difference between groups in ASAS40 response at week 16 was 33.8% (56.7% compared with the placebo group 23.0%; p<0.0001). Since this efficacy variable is considered as at least as important as the chosen primary endpoint ASAS20, a sensitivity test in form of

analysis of the PP population for ASAS40 response at Week 16 was provided by the MAH and the robustness of the results was supported.

The difference between groups in proportion of subjects achieving BASDAI50 was 28.0 (p <0.0001), ASAS Partial remission 15.2% (p<0.0001). The primary analysis of the change from baseline for SPARCC MRI was made on 161 subjects, since 10 subjects did not have baseline MRI, and 26 either missed Week 16 MRI or performed it too late (more than 5 days after the start of part 2). The difference between groups was still significant.

The treatment effects of golimumab 50 mg versus placebo across most of the subgroups based on demographics and baseline disease characteristics were consistent with the treatment effect observed in the FAS population. In the subgroup analysis based on stratification factors, no treatment benefit was observed for subjects with the combination of negative MRI and CRP within normal limits at baseline. Other endpoints that not were met were swollen and tender joint score respectively, or chest wall expansion. This is not unexpected, given the small number of inflamed peripheral joints in this population, (approximately 1.5 swollen and 3-4 tender). For chest wall expansion the MAH proposed that this may not be affected in this relatively early disease. This may be questioned, since the BL mean values are lower than what could be considered normal. However, the clinical significance is limited.

It was noted that there seems to be a difference between males and females in achieving the primary endpoint as compared to placebo. This was seen also for ASAS40. The finding is noteworthy, since there was an imbalance between groups, with fewer females in the golimumab group. A similar outcome pattern has occurred with the age groups ⩽30 and >30. The weighted-average responses for ASAS 20 and ASAS 40, compared with the observed FAS population responses provided by the MAH indicated that the effect of the gender and age imbalance in the treatment assignments had minimal impact on the overall size of the treatment effect.

Of the 69 golimumab 50 mg/golimumab 50 mg subjects who achieved **ASAS 20** response at Week 16, 66 (95.7%) achieved ASAS 20 response at Week 24. The corresponding figure for **ASAS 40** response was 92.7%, for **BASDAI 50** 91.1%, and for **ASAS partial remission** 90.6%. There was thus an acceptable persistence of the results achieved at Week 16.

Four (4.3%) subjects developed antibodies to golimumab through Week 16. All 4 achieved ASAS20 at Week 16. The MAH argued that this suggests that development of immunogenic response had little impact on efficacy and has upon request provided key secondary endpoint results for these patients further supporting this.

The magnitude of effect with golimumab in the OSI population was numerically similar to or greater than what was observed in the overall study population.

2.4.3. Conclusions on the clinical efficacy

One study has been presented, P07642, where 50mg SC Q4W was tested in comparison to placebo during a 16 week period. After week 16 all remaining subjects are treated open label, and the study is ongoing. The primary efficacy endpoint, the ASAS20 response at Week 16 was statistically significantly greater (p<0.001) in the active group (golimumab [71.1%] compared with the placebo group (40.0%). The difference to placebo (31.2%) is clinically relevant. Further, also the secondary endpoint ASAS40, which is considered more relevant for an anti-TNF agent, was met, with a difference to placebo of approximately 33.8% at week 16. Other secondary analyses also support efficacy. Thus, the study results support the efficacy of golimumab in the nr Axial SpA population, regarding symptoms, spinal mobility and inflammation.

The MAH will conduct a clinical study to evaluate the efficacy of golimumab (full or reduced treatment regimen) versus treatment withdrawal in subjects with nr Axial SpA who have attained inactive disease while receiving open-label golimumab and to characterise the efficacy of golimumab as retreatment upon flare in subjects with nr-Axial SpA (as described in the RMP).

2.5. Clinical safety

Introduction

The safety profile of golimumab is well established as evidenced by available clinical study and post-authorization safety data and approvals of golimumab for AS, PsA, RA, and UC in adults. The most commonly reported ADR in clinical studies is upper respiratory tract infection. The most serious ADRs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome) and haematologic reactions.

The discussion of safety in this submission focused on data in the indication of nr Axial SpA provided by the pivotal Phase 3b study P07642 through the data cutoff of 06 May 2014, the date the last subject completed the Week 24 visit. By that date, safety data were available through the end-of-study Week 60 visit for more than 65% of subjects.

In the submission, safety data from the P07642 study were also presented together with data from the combined AS studies (C0524T09 and C0524T29). In addition, the safety data of P07642 was integrated into the overall golimumab safety database upon which the safety data in the product information is derived.

The safety data from the studies mentioned above were combined and presented in 3 different datasets as described below.

- Presentation 1: comparisons of data from the P07642 study and the combined AS studies dataset. This data presentation focused on the proportions of events for overall AEs (eg, AEs, SAEs, and discontinuations due to AEs) in each study and treatment group.
- Presentation 2 focused on comparisons of data from the P07642 study and the large datasets derived from the combined Phase 3 SC rheumatologic studies (AS, RA, and PsA). This data presentation focused on the incidence of events of interest in each study and treatment group.
- A third data presentation comprised data from the P07642 study and various datasets derived from studies of golimumab in other indications. This data presentation is used to support prescribing safety information and included all indications, both approved and unapproved, with the exceptions of uveitis and Sarcoidosis.

Patient exposure

nr-Axial SpA

Table 18: Subject status in the Phase 3 P07642 study in nr-Axial SpA; randomized subjects (cutoff date 06 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.		

As of 06 May 2014, a total of 193 subjects had received at least 1 dose of golimumab 50 mg; 113 (58.5%) subjects had been exposed to golimumab for >24 weeks to ≤52 weeks, and 68 (35.2%) subjects had been exposed to golimumab for >52 weeks. The exposure was 172 subject-years of follow-up for subjects while receiving golimumab and 31 subject-years of follow-up for subjects while receiving placebo

Combined AS Studies

As of 06 May 2014 in the completed combined AS studies (C0524T09 and C0524T29), a total of 424 subjects had received at least 1 dose of golimumab 50 mg; 130 (30.7%) subjects had been exposed to golimumab 50 mg for >24 weeks to ≤52 weeks, and 251 (59.2%) subjects had been exposed to golimumab 50 mg for >52 weeks. The exposure was 1644 subject-years of follow up for subjects while receiving golimumab and 68 subject years of follow-up for subjects while receiving placebo.

Phase 3 SC Rheumatologic Studies and UC

Data from the pooled Phase 3 SC studies in rheumatologic indications and UC includes 10 Phase 3 SC studies in rheumatologic indications and UC.

Through the common placebo controlled period in these studies, 1146 subjects received placebo with 271 subject years of follow up and 2702 subjects received golimumab with 651 subject years of follow up. Through the controlled and uncontrolled period in these studies, 1146 subjects received placebo with 557 subject years of follow up and 3661 subjects received golimumab with 10,555 subject years of follow up.

Adverse events

P07642

Treatment with golimumab was generally well tolerated in subjects with nr-Axial SpA, with similar safety profiles observed in the placebo and golimumab 50 mg groups. Through the last data cut-off, no deaths, serious opportunistic infections, active tuberculosis, malignancies, or serious systemic hypersensitivity (including anaphylactic reactions) were reported. Two serious infections were reported in the golimumab group through the last data cut-off.

Key safety results through Week 16 from P07642 are presented in Table 19.

Table19: Overall summary of adverse events through Week 16 (placebo-controlled period) -- treated subjects in P07642

	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

[a] Excludes lymphoma, nonmelanoma, and melanoma

Adapted from: Mod2.7.4/nr-Axial SpA 24-Week SCS, Table 6

Table 20:

Overall summary of adverse events through Week 16 (placebo-controlled period); treated subjects in Phase 3 SC studies in nr-Axial SpA and AS

Table 20: Overall summary of adverse events through Week 16 (placebo-controlled period); treated subjects in Phase 3 SC studies in nr-Axial SpA and AS

	P07642 nrAxSpA Study[a]		C0524T09			Combined AS Studies[b]			Combined nrAxSpA and AS studies		
	Placebo	Golimumab 50mg	Placebo	Golimumab 50mg	Golimumab 100mg	Placebo	Golimumab 50mg[c]	Golimumab 100mg[d]	Placebo	Golimumab 50mg	Golimumab 100mg
Treated subjects in Phase 3 SC studies of AS and nrAxSpA	100	97	77	138	140	182	246	140	282	343	140
Avg duration of follow-up (weeks)	16.0	15.9	16.0	16.1	16.0	15.9	16.0	16.0	16.0	16.0	16.0
Avg exposure (number of administrations)	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9
Subjects with 1 or more adverse events	46[f] (46.0%)	40 (41.2%)	58 (75.3%)	110 (79.7%)	109 (77.9%)	91 (50.0%)	144 (58.5%)	109 (77.9%)	137 (48.6%)	184 (53.6%)	109 (77.9%)
Subjects who discontinued study agent because of 1 or more adverse events	1 (1.0%)	2 (2.1%)	1 (1.3%)	4 (2.9%)	3 (2.1%)	1 (0.5%)	5 (2.0%)	3 (2.1%)	2 (0.7%)	7 (2.0%)	3 (2.1%)
Subjects with 1 or more serious adverse events	2 (2.0%)	1 (1.0%)	5 (6.5%)	6 (4.3%)	8 (5.7%)	5 (2.7%)	7 (2.8%)	8 (5.7%)	7 (2.5%)	8 (2.3%)	8 (5.7%)
Deaths	0	0	0	0	0	0	0	0	0	0	0
Subjects with 1 or more infections[e]	23 (23.0%)	24 (24.7%)	25 (32.5%)	53 (38.4%)	57 (40.7%)	46 (25.3%)	72 (29.3%)	57 (40.7%)	69 (24.5%)	96 (28.0%)	57 (40.7%)
Subjects with 1 or more serious infections[e]	0	0	0	0	2 (1.4%)	0	0	2 (1.4%)	0	0	2 (1.4%)
All malignancies	0	0	1	0	1	1	1	1	1	1	1
Lymphoma	0	0	0	0	0	0	0	0	0	0	0
Melanoma	0	0	0	0	0	0	0	0	0	0	0
Nonmelanoma skin cancer	0	0	1	0	1	1	0	1	1	0	1
Other malignancies[e]	0	0	0	0	0	0	1	0	0	1	0
Subjects with 1 or more injection-site reactions	3 (3.0%)	0	2 (2.6%)	9 (6.5%)	6 (4.3%)	2 (1.1%)	9 (3.7%)	6 (4.3%)	5 (1.8%)	9 (2.6%)	6 (4.3%)

Table 20: Overall summary of adverse events through Week 16 (placebo-controlled period); treated subjects in Phase 3 SC studies in nr-Axial SpA and AS

	P07642 nrAxSpA Study[a]		C0524T09			Combined AS Studies[b]			Combined nrAxSpA and AS studies		
	Placebo	Golimumab 50mg	Placebo	Golimumab 50mg	Golimumab 100mg	Placebo	Golimumab 50mg[c]	Golimumab 100mg[d]	Placebo	Golimumab 50mg	Golimumab 100mg

[a] P07642
[b] C0524T09 and C0524T29
[c] C0524T09 and C0524T29
[d] C0524T09 only
[e] Excludes lymphoma, nonmelanoma, and melanoma

[f] The P07642 CSR table reports 47 subjects with 1 or more AEs. One subject (Subject 0720-00002) had an AE on the Week 16 visit and was included in the P07642 CSR table. For this SCS, any AEs that occurred on the Week 16 visit date were excluded from Week 16 summary table.

Adapted from: [TSFS1A02.rtf]; [TSFS1A03.rtf]; [TSFS1A04.rtf]; [TSFS1A05.rtf]; [TSFS1A06.rtf]; [TSFS1A07.rtf]; [TSFS1A08.rtf]; [TSFS1A09.rtf]; [TSFS1A10.rtf]; [TSFS1A11.rtf]

Table 21 TSFS1A04: Number of subjects with any adverse events with frequency of >=5% occurring in the golimumab group in Study P07642 through Week 16 by MedDRA system-organ class and preferred term; treated subjects		
	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%)
Adapted from Mod5.3.5.3/nr-Axial SpA 24-Week ISS/AppA.3/TSFS1A04		

For all events, it should be noted that, since all subjects were receiving golimumab after Week 16, the average duration of follow-up through the last data cut-off was 16.2 weeks for subjects receiving placebo and 46.2 weeks for subjects receiving golimumab.

Table 22: TSFS1C04: Number of subjects with any adverse events with frequency of >=5% occurring in the golimumab group in Study P07642 through 06 May 2014 by MedDRA system-organ class and preferred term; treated subjects		
	P07642	
	Placebo	Golimumab 50mg
Treated subjects in Phase 3 SC study of nrAxSpA	100	193
Avg duration of follow-up (weeks)	16.2	46.2
Avg exposure (number of administrations)	3.9	10.1
Subjects with 1 or more adverse events	47 (47.0%)	101 (52.3%)
System-organ class/preferred term		
Infections and infestations	23 (23.0%)	69 (35.8%)
Nasopharyngitis	9 (9.0%)	24 (12.4%)
Upper respiratory tract infection	2 (2.0%)	13 (6.7%)
Influenza	5 (5.0%)	12 (6.2%)
Musculoskeletal and connective tissue disorders	7 (7.0%)	17 (8.8%)
Gastrointestinal disorders	16 (16.0%)	26 (13.5%)
General disorders and administration site conditions	12 (12.0%)	14 (7.3%)
Skin and subcutaneous tissue disorders	6 (6.0%)	20 (10.4%)
Nervous system disorders	11 (11.0%)	23 (11.9%)
Headache	6 (6.0%)	17 (8.8%)
Respiratory, thoracic and mediastinal disorders	8 (8.0%)	16 (8.3%)

Table 22: TSFS1C04: Number of subjects with any adverse events with frequency of >=5% occurring in the golimumab group in Study P07642 through 06 May 2014 by MedDRA system-organ class and preferred term; treated subjects		
	P07642	
	Placebo	Golimumab 50mg
Injury, poisoning and procedural complications	4 (4.0%)	15 (7.8%)
Adapted from Mod5.3.5.3/nr-Axial SpA 24-Week ISS/AppA.9/TSFS1C04		

Serious adverse event / deaths / other significant events

SAEs

Through Week 16, there were 3 subjects with 1 or more SAEs: 2 subjects (2.0%) in the placebo group (back pain and cholelithiasis) and 1 subject (1.0%) in the golimumab 50 mg group (foetal death in the female partner of a male subject.

Through the last data cut-off, a total of 8 subjects reported 1 or more SAEs, including 6 subjects receiving golimumab (3.1%;). SAEs reported after Week 16 were duodenitis, uterine polyp, staphylococcal infection, bacterial infection, and migraine.

Deaths

Through the last data cut-off, there were no deaths in the P07642 study in nr-Axial SpA.

Other significant events

Analyses of events of interest were performed for certain events (infections, serious infections, infections of interest, demyelination, malignancies, congestive heart failure, major adverse cardiovascular events [MACE], hypersensitivity reactions, serum sickness, anaphylactic reactions, and clinically important hepatobiliary events). These incidence rates are calculated based on the duration of the safety follow up, expressed as incidence per 100 subject-years to adjust for differences in safety follow-up.

Serious infections

Through Week 16, there were no serious infections in the placebo or golimumab 50 mg groups in the P07642 study and combined AS studies.

Through the last data cutoff, there were 2 subjects in the golimumab 50 mg group in the P07642 study reporting 1 or more serious infections. The incidence of serious infections per hundred subject-years of follow-up through the last data cutoff in the P07642 study was 0.00 (95% CI: 0.00, 9.59) in the placebo group and 1.17 (95% CI: 0.14, 4.21) in the golimumab 50 mg group.

The incidence of serious infections per hundred subject-years of follow-up through the last data cutoff in the combined P07642 and AS studies was 1.01 (95% CI: 0.03, 5.64) in the placebo group and 1.39 (95% CI: 0.78, 2.30) in the golimumab 50 mg group.

Infections of Interest

Through the last data cutoff, there were no events of sepsis, opportunistic infections or Tuberculosis.

Pneumonia

Through the last data cutoff in the P07642 study, there were 2 events of pneumonia in the golimumab 50 mg group. The incidence of pneumonia per 100 subject-years was 0.00 (95% CI: 0.00, 9.59) in the placebo group and 1.17 (95% CI: 0.14, 4.21) in the golimumab 50 mg group.

In the combined P07642 study and AS studies, the incidence of pneumonia per 100 subject-years was 0.00 (95% CI: 0.00, 3.03) in the placebo group and 0.84 (95% CI: 0.38, 1.59) in the golimumab group with overlapping CIs.

Cellulitis

Through the last data cutoff, there was 1 event of cellulitis in the golimumab 50 mg group in the P07642 study. The incidence of cellulitis per 100 subject-years in the P07642 study was 0.00 (95% CI: 0.00, 9.59) in the placebo group and 0.58 (95% CI: 0.01, 3.25) in the golimumab group.

In the combined AS studies, 7 events of cellulitis occurred in the golimumab 50 mg group and 14 events occurred in the golimumab 100 mg group (all events occurred in the C0524T09 study). The incidence of cellulitis per 100 subject-years in the P07642 study and combined AS studies was 0.00 (95% CI: 0.00, 3.03) in the placebo group and 0.74 (95% CI: 0.32, 1.47) in the golimumab 50 mg group with the CI for the golimumab group contained within the CI for placebo group.

Malignancies other than skin cancers

Through the last data cut-off, there were no malignancies in the P07642 study.

Skin cancers

Through the last data cut-off there were no cases of melanoma across the P07642 study and combined AS studies. There were no cases of NMSC in the P07642 study.

Demyelination

Through the last data cut-off, there were no events of demyelination in the P07642 study.

Congestive Heart Failure

Through the last data cut-off, there were no events of CHF in the P07642 study.

Major Adverse Cardiovascular Events

Through the last data cut-off, there were no events of MACE in the P07642 study.

Hypersensitivity Reactions

Through Week 16, there were no subjects with hypersensitivity reactions in the P07642 study. In the combined AS studies, there were 3 hypersensitivity reactions in the C0524T09 study.

Through the last data cut-off, there were 2 subjects with hypersensitivity reactions in the golimumab 50 mg group in the P07642 study.

The incidence of hypersensitivity reactions per hundred subject-years of follow-up through the last data cutoff in the P07642 study was 0.00 (95% CI: 0.00, 9.59) in the placebo group and 1.17 (95% CI: 0.14, 4.21) in the golimumab 50 mg group

The incidence of hypersensitivity reactions per hundred subject-years of follow-up through the last data cutoff in the P07642 study and combined AS studies was 0.00 (95% CI: 0.00, 3.03) in the placebo group and 1.12 (95% CI: 0.58, 1.95) in the golimumab 50 mg group with the CI for the golimumab 50 mg group contained within the CI for placebo group.

Serum Sickness and Anaphylactic Reactions

Through the last data cut-off, there were no subjects with any anaphylactic or serum sickness-like reactions in the P07642 study

Clinically Important Hepatobiliary Events

A clinically important hepatobiliary AE was defined as an elevation of ALT ≥3 x 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.

Through the last data cut-off, there were no clinically important hepatobiliary events in the P07642 study.

Injection-site Reactions

Through Week 16 in the P07642 study, there were 3 (3.0%) subjects with 1 or more injection site reactions in the placebo group and none in the golimumab 50 mg group.

Through the last data cutoff in the P07642 study, there were 3 (3.0%) subjects with 1 or more injection-site reactions in the placebo group and 4 (2.1%) subjects in the golimumab 50 mg group. There were 8 injections (0.4%) with injection site reactions in the golimumab 50 mg group with an average of 10.1 administrations.

In the combined AS studies, there were 2 subjects (1.1%) in the placebo group and 27 subjects (6.4%) in the golimumab 50 mg group with 1 or more injection-site reactions. There were 123 injections (0.8%) with injection-site reactions in the golimumab 50 mg group with an average of 26.0 administrations.

The most common injection site reaction in the P07642 study was injection-site pain, and the most common injection site reaction in the combined AS studies was injection-site erythema.

Antibodies to Golimumab and Adverse Reactions

The relationship between the incidence of antibodies to golimumab and adverse events was assessed in the P07642 study. Following treatment with golimumab 50 mg, 4 subjects had samples at Week 16 which tested positive for anti-golimumab antibodies. One of these 4 subjects positive for anti-golimumab antibodies had an AE of vertebral artery occlusion, which was mild in intensity and resolved.

Analyses to support prescribing safety information

Analyses of events of interest across the nr-Axial SpA P07642 study, Phase 3 SC studies in rheumatologic indications (RA, PsA, and AS), and Phase 3 UC studies were conducted to support prescribing safety information. For these analyses, “All Indications” includes studies in nr-Axial SpA, AS, PsA, RA, and UC as described above.

To assess for changes in the frequency of existing ADRs in the product information, an analysis of AEs across indications through the placebo-controlled period was performed. If the ADR did not occur during the placebo-controlled portion of the studies, the frequencies were determined using longer-term data.

Based on these evaluations, the frequency for the following ADRs in the product information changed*:

- Opportunistic infections: 4/4215 (0.09%)
    - Changes from Uncommon to rare
- Bacterial arthritis: 4/4215 (0.09%)
    - Changes from Uncommon to rare

Laboratory findings

Haematology

Through Week 16 in the P07642 study, there were 2 subjects with any markedly abnormal hematology values. In the placebo group, 1 subject had an elevated white blood cell count (WBC) and 1 subject had elevated absolute eosinophils. Through Week 24 one subject in the golimumab 50 mg group had >1 abnormal value for decreased absolute lymphocytes.

Through the last data cut-off in the P07642 study, the number of subjects with any markedly abnormal hematology value remained low.

Clinical Chemistry

Markedly Abnormal Chemistry Values

Through Week 16 in the P07642 study, there were 4 subjects with any markedly abnormal chemistry values, with elevated potassium and elevated total bilirubin being the only abnormal chemistry values. There were no subjects in the P07642 study with >1 abnormal chemistry value.

Through the last data cut-off in the P07642 study, the number of subjects with any markedly abnormal chemistry value (elevated potassium, elevated ALT, and elevated total bilirubin) remained low. The number of subjects with >1 abnormal chemistry value (elevated total bilirubin) also remained low.

Maximum Postbaseline ALT/AST Elevations

Through Week 16 in the P07642 study, of the subjects with a baseline ALT ≤ ULN, 3.1% (3 subjects) in the placebo group and 7.7% (7 subjects) in the golimumab group had an ALT >1 to <2 × ULN. Of the subjects with a baseline ALT ≤ ULN, none of the subjects in the placebo group and 3.3% (3 subjects) in the golimumab group had an ALT ≥2 to <3 × ULN. Through Week 16, no subjects in the P07642 study had an elevated ALT ≥3 × ULN irrespective of baseline ALT levels.

The incidence of postbaseline ALT elevations >1 to <3 x ULN per hundred subject-years of follow-up through the last cutoff in the P07642 study was 25.62 (95% CI: 11.06, 50.48) in the placebo group and 39.04 (30.25, 49.57) in the golimumab 50 mg group with the CI for the golimumab 50 mg group contained within the CI for placebo group.

The incidence of postbaseline ALT elevations >1 to <3 x ULN per hundred subject-years of follow-up through the last cut-off in the combined AS studies was 51.60 (95% CI: 38.42, 67.85) in the placebo group and 55.95 (51.57, 60.60) in the golimumab 50 mg group with the CI for the golimumab 50 mg group contained within the CI for placebo group.

Safety in special populations

Through the last data cut-off, in the P07642 study and combined AS studies, there was no discernable effect of demographics (gender, race, weight, age) on the proportions of subjects with AEs

As of 06 Apr 2014, a total of 169 pregnancies had been reported in patients or partners of patients treated with golimumab from clinical trials and the postmarketing setting.

In the P07642 study through the last data cutoff (06 May 2014), there was 1 pregnancy reported in the partner of a subject who received golimumab 50 mg. The female partner of Subject 201000007/114809 in the golimumab 50 mg group experienced a spontaneous abortion (reported as fetal loss) at less than 20 weeks. Conception was prior to subject starting golimumab.

Safety related to drug-drug interactions and other interactions

No formal studies of drug-drug interactions were performed with golimumab.

Discontinuation due to adverse events

Through Week 16 (the placebo-controlled period), in the P07642 study (1.0% [1 subject] in the placebo group and 2.1% [2 subjects] in the golimumab 50 mg group) discontinued study agent because of 1 or more adverse events compared with the combined AS studies (0.5% [1 subject] in the placebo group and

2.0% [5 subjects] in the golimumab 50 mg group) and C0524T09 (1.3% [1 subject] in the placebo group and 2.9% [4 subjects] in the golimumab 50 mg group).

The SOC with the highest proportions of AEs leading to discontinuation of study agent was Investigations; however, most events occurred once with no discernable pattern in the types of AEs or evidence of a dose response.

In the P07642 study (2.6% [5 subjects] in the golimumab 50 mg group) discontinued study agent because of 1 or more adverse events compared with the combined AS studies (3.3% [14 subjects] in the golimumab 50 mg group) and C0524T09 (5.6% [12 subjects] in the golimumab 50 mg group).

Post marketing experience

The MAH points out that no postmarketing data in the indication of nr-Axial SpA is available for golimumab. The postmarketing safety profile of golimumab is closely monitored and reported on an ongoing basis via the Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR). The Applicant's routine pharmacovigilance activities include systematic collection of AEs from multiple sources and real-time and periodic medical assessments of single and aggregate cases to identify potential safety signals. As of 06 Apr 2014, an estimated 224,116 patients have been exposed to commercial golimumab worldwide since launch (Golimumab Periodic Benefit-Risk Evaluation Report-Periodic Safety Update Report [PBRER-PSUR], 07 April 2013 to 06 April 2014).

2.5.1. Discussion on clinical safety

The MAH has presented safety data for the nr-Axial SpA indication from the pivotal study P07642. As supportive analyses, safety data from this study were compared with data from the safety database for golimumab in other indications. Of these, AS is of the greatest interest, given the close similarities between the affected populations.

Safety data from the P07642 study was presented through week 16, 24 and the last data cut-off point, which was 06 May 2014. As of that date, the last subject had completed 24 weeks. A total of 193 subjects had received at least 1 dose of golimumab 50 mg; 113 (58.5%) subjects had been exposed to golimumab for >24 weeks to ≤52 weeks, and 68 (35.2%) subjects had been exposed to golimumab for >52 weeks.

No new adverse drug reactions were identified in the safety data from study 07642. As could be expected, the most common AEs occurred within the SOC Infections and infestations (23.0% in the placebo group and 24.7% in the golimumab group (through week 16). The most common PT was nasopharyngitis followed by upper respiratory tract infection. The corresponding results in the combined AS studies were 22.0% in the placebo group and 28.9% in the golimumab 50 mg group. The SOC with the second most frequently reported AEs was gastrointestinal disorders ,15.0% in the placebo group and 8.2% in the golimumab 50 mg group in the P07642 study and 11.5% in the placebo group and 16.3% in the golimumab 50 mg group in the combined AS studies.

During the placebo-controlled period, i.e. the first 16 weeks of the study, 1 SAE emerged in the golimumab treated group. This was a foetal death in the female partner of a male subject, who had not yet been exposed to golimumab by the time of conception. By the last data cutoff, 5 additional subjects in the golimumab group had experienced 1 or more SAEs (duodenitis, uterine polyp, staphylococcal infection, bacterial infection, and migraine). This corresponds to 3.1% of the subjects randomized to golimumab. In the combined AS studies, 9.0% (38 subjects) of the golimumab 50 mg group had 1 or more SAEs through the last data cut-off.

There were no malignancies, TB infections, cases of sepsis or opportunistic infections, events of demyelination, events of congestive heart failure, MACE, clinically important hepatobiliary events, or

anaphylactic or serum sickness-like reactions observed in the Phase 3 P07642 nr-Axial SpA study through the last data cut-off.

Through the last data cut-off in the P07642 study (2.1% [4 subjects] in the golimumab 50 mg group) discontinued study agent because of 1 or more adverse events compared with the combined AS studies (1.7% [6 subjects] in the golimumab 50 mg group) and C0524T09 (2.2% [4 subjects] in the golimumab 50 mg group).

Based upon the additional data provided from the P07642 study, the MAH proposed to update the product information for frequency of 2 AEs, “opportunistic infections” and “bacterial arthritis”. Both ADRs would be classified as rare instead of uncommon. This update is endorsed by the CHMP.

2.5.2. Conclusions on clinical safety

No new significant safety signal has emerged in study P07642. The MAH also refers to the existing AS, RA and UC safety data bases, and has provided comparisons between the safety results from the current nr-Axial SpA and combined AS studies, as well as to combined rheumatologic studies and all combined golimumab studies.

Upon review of the submitted data, it is concluded that the adverse event (AE) incidence and profile of golimumab in the nr-Axial SpA-population was as expected for an anti-TNF-therapy and consistent with previous experience with golimumab.

There is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the safety and efficacy of retreatment after disease flare. The MAH will conduct a clinical study to evaluate the safety of golimumab as re treatment for a disease-activity flare in subjects who have been able to withdraw treatment for nr-Axial SpA after attaining inactive disease (as described in the RMP).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.1 is acceptable.

The RMP was updated to include data on nr-Axial SpA and performed studies in relevant sections of the RMP while no changes to the Summary of safety concerns (Part II, Module SVIII), the Pharmacovigilance Plan (Part III) nor the Risk Minimisation measures (Part V) were implemented.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, changes related to section 4.8, “Description of selected adverse reactions” of the SmPC has been updated with regard to incidence numbers. Further, the table in section 4.8 has been updated regarding the frequency of “Opportunistic infection” and “Bacterial arthritis”, both changed from Uncommon to Rare. This was endorsed by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

One study has been presented, P07642, where 50mg SC Q4W was tested in comparison to placebo during a 16 week period. After week 16 all remaining subjects are treated open label, and the study is ongoing.The primary efficacy endpoint, the ASAS20 response at Week 16 was statistically significantly greater ($p<0.001$) in the active group (golimumab [71.1%] compared with the placebo group (40.0%). The difference to placebo (31.2%) is clinically relevant. Further, also the secondary endpoint ASAS40, which is considered more relevant for an anti-TNF agent, was met, with a difference to placebo of approximately 33.8% at week 16. Other secondary analyses also support efficacy. Thus, the study results support the efficacy of golimumab in the nr Axial SpA population, regarding symptoms, spinal mobility and inflammation.

Uncertainty in the knowledge about the beneficial effects

There is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the safety and efficacy of retreatment after disease flare. The MAH will conduct a clinical study to evaluate the efficacy of golimumab (full or reduced treatment regimen) versus treatment withdrawal in subjects with nr Axial SpA who have attained inactive disease while receiving open-label golimumab and to characterise the efficacy of golimumab as retreatment upon flare in subjects with nr-Axial SpA (as described in the RMP).

Risks

Unfavourable effects

The safety profile of golimumab is well established and is characterised by several potentially serious risks, including but not limited to infections and potential risks of malignancies, congestive heart failure and demyelinating disorders. Adequate risk minimisation as well as pharmacovigilance activities are in place from previous procedures, and are adequate to also cover the current indication.

No new safety signal has emerged in study AS001. The MAH also refer to the AS safety data base, and the safety profile appears not unexpectedly to be similar between the populations.

Uncertainty in the knowledge about the unfavourable effects

Further long term safety data is still missing and will be gathered in the ongoing studies in other indication which include long term outcomes as described in the RMP.

There is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the safety of retreatment after disease flare. The MAH will conduct a clinical study to evaluate the safety of golimumab as re treatment for a disease-activity flare in subjects who have been able to withdraw treatment for nr-Axial SpA after attaining inactive disease (as described in the RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The disease nr Axial SpA is a painful condition with a considerable negative impact on function and work productivity in the afflicted patients.

The diagnostic criteria are based on the presence of back pain for more than 3 months, and either MRI findings indicative of sacroiliitis or positive HLA B27 in combination with specified clinical features. In the absence of MRI-findings patients without objective measure of inflammation may thus be diagnosed. The safety profile of an anti-TNF agent can be potentially serious and it is important to avoid overtreatment. It is therefore appreciated that the proposed indication includes only patients with either positive MRI findings or elevated CRP. Although the group was small, the subgroup without positive MRI and normal CRP levels did not achieve a higher response rate of ASAS20 as compared to the placebo group.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The presented results show efficacy for Simponi in patients with axial spondyloarthritis, and an acceptable safety profile for the right patient population, i.e. those with objective signs of inflammation.

There is very limited knowledge on how long treatment should be continued in subjects in whom there is no disease activity following treatment, or the safety and efficacy of retreatment after disease flare. The MAH will therefore conduct a clinical study to evaluate the efficacy of golimumab (full or reduced treatment regimen) versus treatment withdrawal in subjects who have attained inactive disease while receiving open-label golimumab and the efficacy and safety of golimumab as re-treatment for a disease-activity flare in subjects who have been able to withdraw treatment for nr-Axial SpA after attaining inactive disease (as described in the RMP).

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

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include a new indication for the treatment of non radiographic axial spondyloarthritis (nr Axial SpA) for Simponi (Golimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance.

In addition, the MAH took the opportunity to correct some minor editorial mistakes in the Product Information .

The requested variation proposed amendments to the SmPC and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new indication for the treatment of non radiographic axial spondyloarthritis (nr Axial SpA) for Simponi (Golimumab). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the scientific discussion Simponi-H-C-992-II-61.