25 July 2013
EMA/640422/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Simponi

International non-proprietary name: golimumab

Procedure no. EMEA/H/C/000992/II/39

Note

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

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List of abbreviations

5-ASA - 5-aminosalicylate
6-MP - 6-mercaptopurine
AE - adverse event
ANA - antinuclear antibodies
AS - ankylosing spondylitis
AZA – azathioprine
CHF - congestive heart failure
DB – double-blind
HSTCL - hepatosplenic T-cell lymphoma
IBD - inflammatory bowel disease
IV – intravenous
LLOQ – Lower Limit of Quantification
MedDRA - Medical Dictionary for Regulatory Activities
PK – Pharmacokinetics
PopPK – Population Pharmacokinetics
PsA - psoriatic arthritis
RA - rheumatoid arthritis
RMP - risk management plan
SC – subcutaneous
SAEs - serious adverse events
SOC - system organ class
TB - tuberculosis
TNF-α - tumour necrosis factor alpha
UC - ulcerative colitis
ULN - upper limit of the normal range
q4w – every fourth week

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 July 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Simponi	golimumab	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a	*Addition of a new therapeutic indication or modification of an approved one*	II

The MAH applied for a new indication for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. 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 SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0106/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0106/2012 was not yet completed as some measures were deferred.

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 appointed by the CHMP was: Dr. K. Dunder

Submission date:	11 July 2012
Start of procedure:	22 July 2012
Rapporteur's preliminary assessment report circulated on:	14 September 2012
PRAC RMP advice and assessment overview adopted by PRAC	04 October 2012
Rapporteur's updated assessment report circulated on:	12 October 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	21 December 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 January 2013
PRAC RMP advice and assessment overview adopted by PRAC	7 February 2013
Rapporteur's updated assessment report on the MAH's responses circulated on:	14 February 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 February 2013
MAH's responses submitted to the CHMP on:	26 April 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 May 2013
PRAC RMP advice and assessment overview adopted by PRAC	13 June 2013
Updated Rapporteur's assessment report on the MAH's responses circulated on:	20 June 2013
3rd Request for supplementary information adopted by the CHMP on:	27 June 2013
MAH's responses submitted to the CHMP on:	03 July 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 July 2013
CHMP opinion:	25 July 2013

2. Scientific discussion

2.1. Introduction

TNFα is considered a key inflammatory mediator that exhibits a wide variety of functional activities. Abnormally high levels of TNFα have been implicated in the pathophysiology of several immune-mediated diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Binding of TNFα by an anti-TNFα antibody prevents the target from binding to cell surface TNFα receptors and consequently prevents downstream signalling cascades and the deleterious effects of inappropriate or excessive TNFα expression.

In the EU, Simponi is available as a 50 mg Solution for injection in prefilled Pen and Solution for injection in prefilled syringe and is to be administered subcutaneously. The approved indications are:

Rheumatoid arthritis (RA)
Simponi, in combination with methotrexate (MTX), is indicated for:
- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.
Simponi, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Psoriatic arthritis (PsA)
Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Simponi has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

This Type II variation application has been submitted to seek approval of a new therapeutic indication for golimumab i.e. “treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies”.

The application is based on the results of one induction study C0524T17 and of one maintenance study, C0524T18. A long-term extension of study C0524T18 is ongoing through week 228.

A second induction study, study C0524T16, was stopped due to lack of efficacy of single IV induction doses as compared with SC induction in study C0524T17. Efficacy results from this study are not used for support of the UC indication, although PK and safety data from the study is presented.

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

GCP

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

The applicant 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.

On 20th June 2013, the MAH informed the CHMP about misconduct at one study site (site 7407). The CHMP therefore asked the MAH to submit results from all analyses of importance for the evaluation of the efficacy and safety of Simponi in the new indication, comparing the initial study population and the population where these subjects were omitted. Further to this assessment the MAH excluded efficacy data from 10 of 771 patients in the original primary analysis population of the induction study and from 7 of 463 the original primary analysis population of the maintenance study. The new analyses

show that the overall effects of removing the data from this site affect the key efficacy outcomes by 0-1%. The CHMP therefore concluded that data from the new analyses do not change the conclusions on the efficacy results.

The MAH performed additional source data monitoring at seventeen (17) high-enrolling sites in order to assess if further audits were necessary. These sites were chosen based on a risk-assessment algorithm developed by the MAH. The monitoring visits included a thorough assessment of source data for all key efficacy outcomes including a review of the Mayo diary cards, Mayo score calculation, and endoscopy reports at each site. No further cases of misconduct or data integrity issues were identified. Therefore, additional audits were not considered necessary.

At CHMP's request The MAH also confirmed that previously identified non-compliance issues related to the Simponi UC program, including misconduct, were thoroughly investigated and described in the CSRs submitted with this application. The types of observations found at site 7407 were not observed at any other sites in the program.

- Tabular overview of clinical studies

Table 1: Listing of golimumab clinical studies summarized in this SCP

Study ID	Population	Dose Regimen	Route of Administration	Number of Subjects Treated	Sampling Scheme[a]
Phase 2/3 UC Studies					
C0524T16 (induction)	UC	1 mg/kg 2 mg/kg 4 mg/kg placebo single dose	IV	290	Sparse
C0524T17 (induction)	UC	100 mg → 50 mg 200 mg → 100 mg 400 mg → 200 mg placebo → placebo Week 0 and 2 dose administration	SC	1064	Sparse
C0524T18[b] (maintenance)	UC	50 mg 100 mg placebo q4w	SC	1228[c]	Sparse
Phase 1 Studies					
CNTO148NAP1001	HS	200 mg 400 mg placebo single dose	SC	49	Intensive
C0524T23	HS	50 mg 100 mg single dose	SC	51	Intensive
C0524T15	HS	100 mg single dose	SC or IV	78	Intensive
C0524T14	RA	100 mg q4w 2 mg/kg on Day 1 and Day 85	SC IV	49	Intensive

2.3.2. Pharmacokinetics

The role of pharmacokinetics in this application was to describe the PK of the new dose level (100 mg) and the new patient group (UC).

Pharmacokinetic sampling was performed in all three studies performed in UC:

- C0524T16 IV induction study

- C0524T17 SC induction study

- C0524T18 SC maintenance study

The studies and results are described below. The data was also used to perform a population PK analysis.

In addition, four phase I studies (CNTO148NAP1001, C0524T23, C0524T15 and C0524T14) in healthy volunteers and RA patients are referred to.

Introduction

The doses for the clinical studies in UC were chosen based on clinical data of infliximab and knowledge about the relative potency of infliximab and golimumab, since the use of infliximab is already established in UC.

Phase 2/3 studies in UC

- **Analytical methods**

Serum golimumab concentrations were measured using an electrochemiluminescent immunoassay (ECLIA), in two versions, a bead-based method on a BioVeris platform in C0524T23 and C0524T15, and a plate-based method on a Meso Scale Discovery (MSD) platform in C0524T14, CNTO148NAP1001, C0524T16, C0524T17, and C0524T18. The BioVeris assay has been assessed previously. The MSD method has shown comparable results to the BioVeris assay, when analysing incurred study samples and controls using the ECLIA (MSD) assay, 54 of the 60 samples were within ± 30% of the corresponding BioVeris ECLIA results.

- **Pharmacokinetic data analysis**

A population PK analysis was performed to characterize the PK of golimumab and evaluate the influences of subject demographic characteristics and other intrinsic or extrinsic factors on the disposition of golimumab in subjects with UC.

- **Study design**

C0524T16 was a Phase 2/3 multicenter, dose-ranging (Part 1), dose-confirming (Part 2), randomized, double-blind, placebo-controlled, parallel-group study of the safety and efficacy of IV induction regimens of golimumab in subjects with moderately to severely active UC. Doses of 1 mg/kg, 2 mg/kg, 4 mg/kg or placebo were administered at Week 0. At study termination, a total of 291 subjects had been randomized to treatment, 214 subjects to golimumab (62, 75, and 77 subjects to the 1 mg/kg, 2 mg/kg, and 4 mg/kg groups, respectively) and 77 subjects to placebo. Serum samples for the measurement of golimumab concentrations were drawn before and 1 hour after a single golimumab infusion was administered at Week 0. Samples were also collected at Weeks 2, 4, and 6. An additional sample was collected 16 weeks after the last administration of study agent for subjects who terminated the study and did not continue into the maintenance study (C0524T18).

C0524T17 was a Phase 2/3 multicenter, dose-ranging (Part 1), dose-confirming (Part 2), randomized, double-blind, placebo-controlled, parallel-group study of the safety and efficacy of SC induction regimens of golimumab in subjects with moderately to severely active UC. Doses of 100 mg and 50 mg, 200 mg and 100 mg or 400 mg and 200 mg or placebo were administered at Week 0 and Week 2 respectively. A total of 1,065 subjects were randomized to treatment, 734 subjects to golimumab (72, 331, and 331 subjects to 100 mg and 50 mg, 200 mg and 100 mg, and 400 mg and 200 mg,

respectively) and 331 subjects to placebo. Serum samples for the measurement of golimumab concentrations were collected before drug administration at Weeks 0 and 2. Samples were also collected at Weeks 4 and 6. An additional sample was collected 16 weeks after the last administration of study agent for subjects who terminated the study and did not continue into the maintenance study (C0524T18).

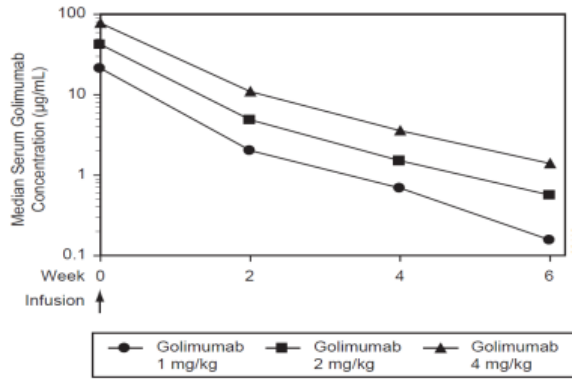
C0524T18 was a Phase 3 multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of golimumab maintenance therapy, administered subcutaneously, in subjects with moderately to severely active UC. Doses of 50 mg, 100 mg or placebo were administered every 4 weeks through Week 52. A total of 464 subjects were randomized to treatment, 308 subjects to golimumab (154, and 154 subjects to 50 mg and 100 mg, respectively) and 156 subjects to placebo. Subjects who achieved clinical response with golimumab in an induction study (i.e., randomized subjects) but who subsequently lost clinical response at any time during C0524T18 were eligible for a single dose adjustment through Week 52. Serum samples for the measurement of golimumab concentrations were collected prior to study agent administration at Weeks 4, 8, 12, 20, 28, 36 and 44. Additional samples were also collected at a visit between Weeks 16 and 24 and at Weeks 30 and 54.

- **Study results**

Study C0524T16

In this study, golimumab was administered intravenously at three different dose levels (1, 2 and 4 mg/kg). It was prematurely stopped because of better results from the SC induction study (C0524T17), but included 291 subjects. Serum PK samples were collected at each scheduled visit through week 6.

Figure 1 Median serum golimumab concentration over 6 weeks after a single IV dose of Simponi 1 (n=63), 2 (n=74) and 4m (n=76) mg/kg.

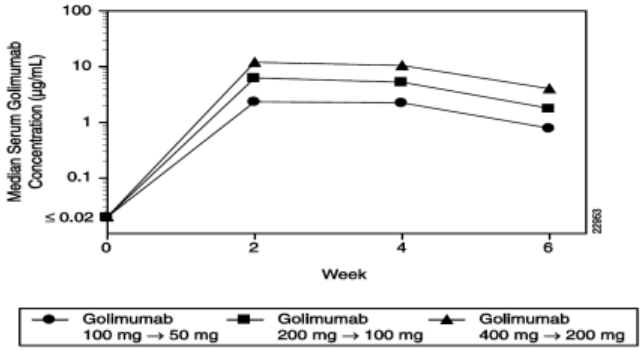


The median serum golimumab levels at 6 weeks were 0.16, 0.56 and 1.40 µg/ml after single dose IV administration of 1, 2 and 4 mg/kg, respectively. 27% of the patients receiving 1 mg/ml, 11% receiving 2 mg/kg and none in the high dose group had undetectable levels (<0.03905 µg/ml) at week 6. None of the patients were positive for golimumab antibodies.

Study C0524T17

In this study, golimumab was administered SC on week 0 and week 2 at three different dose levels (100 mg + 50 mg, 200 mg + 100 mg, 400 mg + 200 mg). Serum PK samples were collected at each scheduled visit through week 6.

Figure 2. Median serum golimumab concentration over 6 weeks after a two SC doses (week 0 and 2) of Simponi 100+50 (n=71), 200+100 (n=331) and 400+200 (n=332) mg.

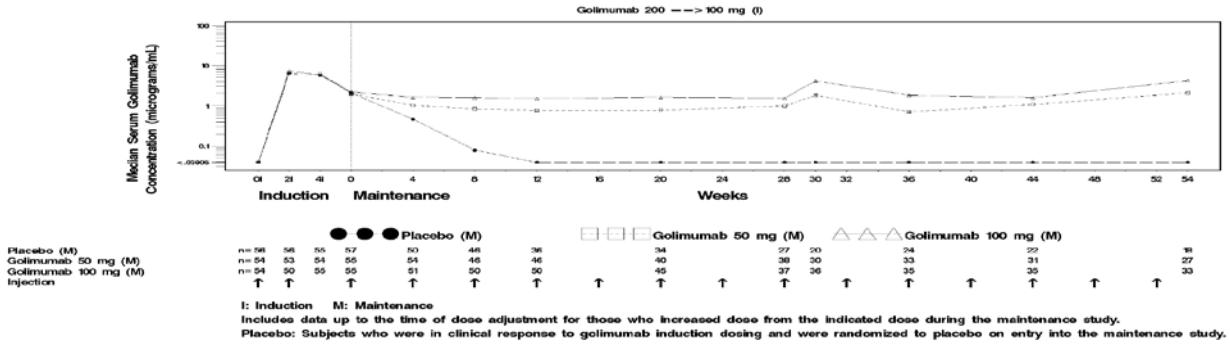


The median serum golimumab levels at 6 weeks were 0.78, 1.78 and 4.01 µg/ml after 2 SC doses of 100+50, 200+100 and 400+200 mg, respectively. Very few patients had undetectable levels (<0.03905 µg/ml) at week 6 (3.4%, 0.3%, and 0.4%). Of the 721 patients, 3 were positive for golimumab antibodies.

Study C0524T18

Steady state was judged to be reached at week 8 (14 weeks from start of induction) and the steady state level was approximately dose proportional (at week 8-44, median drug concentration was 0.69-0.83 µg/ml in the 50 mg dose group and 1.33-1.58 µg/ml in the 100 mg group). Median plasma levels for randomized subjects who had received the 200 + 100 mg SC induction are shown in Figure 3.

Figure 3 Median serum golimumab concentrations (ug/ml) through week 54 of the maintenance study (C0524T18) from week 0 of the induction study (T17) in randomized patients with 200+100 mg SC induction.



At Week 8 of C0524T18, median pre-administration serum golimumab concentrations in subjects who were randomized to placebo from the SC golimumab induction treatment groups were either low (0.39 µg/mL in the 400 mg → 200 mg and 0.08 µg/mL 200 mg → 100 mg groups) or below the limit of quantification (golimumab 100 mg → 50 mg group). In subjects who were randomized to golimumab 100 mg, the median pre-administration serum golimumab concentrations at Week 8 were 1.54 µg/mL, 1.60 µg/mL, and 1.14 µg/mL for subjects receiving golimumab SC induction at 400 mg → 200 mg, 200 mg → 100 mg, or 100 mg → 50 mg, respectively. In subjects who were randomized to golimumab 50 mg, the median pre-administration serum golimumab concentrations at Week 8 were 1.01 µg/mL, 0.85µg/mL, and 0.60 µg/mL for subjects receiving golimumab SC induction at 400 mg → 200 mg, 200 mg → 100 mg, or 100 mg → 50 mg, respectively. In general, steady state was reached approximately 8 weeks after maintenance doses were initiated (i.e., 14 weeks after the start of induction treatment) in randomized subjects from the SC induction treatment groups.

Effect of Immunomodulator Use on Serum Golimumab Concentration

Of the 308 subjects in C0524T18 randomized to golimumab, 30.8% (95 subjects) were receiving immunomodulators at Week 0 of induction (30.2% receiving 6-MP or AZA and 0.6% receiving MTX), and 69.2% (213 subjects) were not receiving immunomodulators (C0524T18 54-week CSR\Tab2).

Median serum golimumab concentrations for randomized subjects receiving golimumab 100 mg were comparable irrespective of baseline immunomodulator use status while median serum golimumab concentrations were slightly but consistently higher across all time points in subjects receiving golimumab 50 mg in combination with immunomodulators compared to those in subjects receiving golimumab 50 mg without immunomodulator use.

Pharmacokinetics in target population (popPK analysis of data from subjects with UC)

Serum golimumab concentration-time data was analyzed using nonlinear mixed-effects modeling methods (NONMEM with FOCE-I). The objectives of the analysis were to quantify population PK model parameters including typical values and random variability and identify covariates which significantly influence golimumab pharmacokinetics in subjects with UC.

The analysis was conducted with data from two induction studies (**C0524T16** and **C0524T17**) and one maintenance study (**C0524T18**) in subjects with UC. A total of 11,280 serum golimumab concentrations from 1,227 UC subjects were included in the population PK analysis. There were ten outlier samples excluded from the analysis. In the population PK dataset, serum golimumab concentrations below limit of quantification (BLQ) were replaced with half of the lower limit of quantification (LLOQ). For this population PK analysis, the first post dose BLQ data within a dosing interval was included in the analysis, while BLQ data in a sample prior to the first administration of the drug along with trailing BLQ data were excluded from the final PopPK data set. Thus, all available BLQ data were not included in the calculation of % BLQ. Of the 11,280 serum golimumab concentration samples in the final population PK analysis dataset, 590 samples (5.2%) were BLQ. These samples were associated with the first BLQ samples within a dosing interval and were set to half of the LLOQ value for the population PK analysis; however, trailing BLQ samples (n= 572) were excluded from the analysis data set.

All significant covariates identified in *previous* population PK analyses of golimumab including:

- body weight,
- C-reactive protein (CRP),
- antibody to golimumab status,
- smoking status,
- subject's sex

were assessed for influence on the PK variability of golimumab. In addition, the following covariates were assessed:

- body surface area,
- lean body mass,
- age,

- albumin,
- white blood cell count,
- estimated creatinine clearance,
- hepatic enzymes,
- Mayo score,
- disease duration,
- race (Caucasians versus non-Caucasians, Japanese versus non- Japanese),
- concomitant use of immunomodulators (azathioprine/6-mercaptopurine/ or methotrexate, AZA/6-MP or MTX).

In general, baseline values of the covariates were used in modeling with the exception of antibody to golimumab status or where otherwise specified. Continuous covariates were normalized to the approximate median or selected reference value of the respective covariate as determined from the dataset. Categorical covariates were entered into the model using index variables (0 or 1) and as a fractional change relative to the reference group (usually assigned a 0). Empirical Bayesian estimates (EBEs) were generated from the estimation step in NONMEM. An exploratory graphical evaluation of covariate- parameter relationships was performed. The shrinkages of PK parameters were taken into consideration while assessing plots based on EBEs. A trend between a covariate and a PK parameter led to direct assessment in NONMEM. Final covariate model selection was conducted using a stepwise backward elimination procedure starting with the “full” covariate model. If the effects of two covariates were highly correlated (r>0.7), it was not considered appropriate to incorporate both covariates on the same parameter in the full model. In such a case, the variable with the highest significance (i.e., largest decrease in objective function value (OFV) from the base model), or better clinical utility was used. In the event that highly correlated covariates were identified for different model parameters (e.g. body weight on CL and body surface area on V2), only one of the correlated covariates was included on the different model parameters.

General goodness-of-fit of the final PK model was evaluated by examining a variety of diagnostic and summary graphics. Model stability was tested through the evaluation of the condition number. The covariance step was implemented with each NONMEM run and standard errors for parameter estimates, along with correlations between parameters, were evaluated. A nonparametric bootstrap approach was used to compute confidence intervals for the PK parameters.

Supporting phase 1 studies

The applicant is also referring to four phase I studies with rich PK sampling.

CNTO148NAP1001 (completed April 2011) was comparing a single SC dose of golimumab (200 or 400 mg) in male Caucasian (n=24) and Japanese (n=25) subjects. Similar mean AUC and half life were observed in the two ethnic groups. The mean AUC inf in Caucasians was 246 ug.day/ml after the 200 mg dose and 535 ug.day/ml after the 400 mg dose, thus golimumab appeared dose-proportional in this range.

Study C0524T23 was previously submitted and assessed the PK profile, tolerability and safety of golimumab single SC dose of 50 and 100 mg, and has been assessed previously. The mean AUC inf in Caucasians was 48 ug.day/ml after a 50 mg dose and 129 ug.day/ml after a 100 mg dose, suggesting approximately dose proportionality.

Study C0524T15 was assessing the absolute bioavailability of SC administration of golimumab in healthy subjects, and has been assessed previously as part of the initial MAA.

Study C0524T14 was assessing the multiple dose PK of golimumab in RA patients after IV and SC administration, and has been assessed previously as part of variation II10 (approved in July 2010).

The study CNTO148NAP1001 and C0524T23 together were used to claim dose proportionality between 50 and 400 mg golimumab SC.

The PK parameters in healthy subjects after rich sampling in study C0524T15 was used to compare golimumab PK in healthy subjects to that in UC patients. In the population PK analysis of data from UC patients, golimumab Cl was estimated to be 0.544 L/day in a 70 kg subject. This value is similar to the Cl of 0.480 L/day for a 70 kg subject determined in study C0524T15. The half lives were also similar between the studies – 10.5 compared with 10.9 days. The MAH is also referring to PK data from RA patients (study C0524T14), where Cl/70 kg was estimated to be 0.535 L/day and half life 13 H and 11 days, with and without concomitant administration of methotrexate.

2.3.3. Pharmacodynamics

Introduction

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder involving the large intestines and the rectum. The diseases is characterised by episodes of increased stool frequency and bloody diarrhoea. TNF-α is considered a key inflammatory mediator that exhibits a wide variety of functional activities and appears to play an important role in the pathogenesis of UC.

Mechanism of action

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of TNF-α to its receptors. There are no new data related to pharmacodynamics in this application.

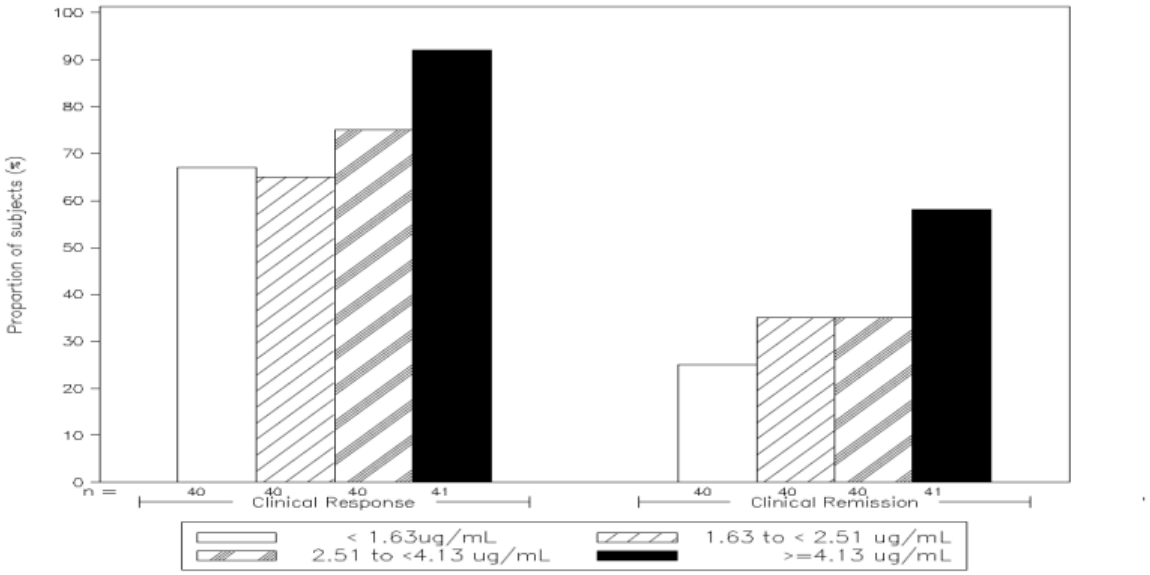
Relationship between plasma concentration and effect

For treated subjects in the phase III maintenance study C0524T18 who were randomized to receive golimumab, the proportions of subjects in clinical response through Week 54 and the proportions of subjects in clinical remission at both Week 30 and Week 54 were summarized by golimumab concentration quartile at Week 54.

The proportion of subjects in clinical response through Week 54 was greatest among subjects in the highest concentration quartile (≥4.13 µg/mL; Figure 4). The proportion of subjects in clinical response through Week 54 was higher in subjects with golimumab concentration of ≥2.51 to <4.13 µg/mL compared with the proportions of subjects with serum golimumab concentrations of ≥1.63 to <2.51 µg/mL and <1.63 µg/mL.

The non-randomized non-responder group had approximately half the median drug levels before receiving the first maintenance dose compared with the randomized responders (1.31 compared with 2.28-2.50 µg/ml).

Figure 4 Bar chart of number of subjects in clinical response through Week 54 or in clinical remission at both Week 30 and Week 54 by serum golimumab concentration; treated subjects who were randomized (excluding site 6706 and site 7257)



2.3.4. Discussion on clinical pharmacology

In study C0524T16 the mean concentration at week 6 was slightly lower than expected assuming dose proportionality. This could be due to limitations in the assay of golimumab and/or non-linear PK due to target mediated drug disposition (which is expected for an IgG-based antibody). Proportionality in exposure is approximately 1 µg/mL. In study C0524T17, dose proportionality was seen for all the doses based on median serum concentrations. In study C0524T18, with the proposed regimen, steady state golimumab levels were reached before week 14 after start of induction and the steady state levels were proportional between the 50 and 100 mg/4 weeks dose group.

The choice of nonlinear mixed effects modeling for the analysis of the data is appropriate. The calculation of the fraction of concentration measurements below limit of quantification (BLQ) was made after exclusion of pre-dose and “trailing” BLQ data. However, the MAH stated that “trailing” BLQ data amounted to n=572 which, together with the BLQ data in the final PopPK data set, would sum up to ~10% of the data. There was a high frequency of BLQ values at week 6 in the 1 mg/kg dose group in study C0524T16 as well as signs of non-proportional relation between doses with respect to median concentration at week 6. This should be viewed from the perspective of target mediated drug disposition which would lead to non-linear PK. Due to the relatively large number of BLQ values in the information rich part of the plasma concentration time profile, non-linear disposition may be obscured. The MAH does not seem to have explored this possibility during the structural model building phase. However, due to limitations of the bioassay, the low concentrations of golimumab may be subject to bias and detection of the potential non-linearity in PK difficult to perform.

The method for covariate modeling which consisted of inclusion based on graphical exploration and significance testing in NONMEM followed by backward deletion from the tentative “full” model is sensitive to shrinkage which was reported to range from 17.7% for ETA2 (CL) to 44.7% for ETA1 (V2). However, a large number of covariates were included in direct significance testing in NONMEM which means that in practice a forward inclusion-backward deletion method was performed, at least for covariate effects on golimumab clearance. This partly mitigates the negative impact of shrinkage on this analysis.

Data from the two phase I studies indicate approximate dose proportionality of golimumab in the dose range 50-400 mg, but in line with what was observed in study C0524T16, slightly lower AUC than expected assuming dose proportionality was observed for the lowest dose. This could be due to limitations in the bioassay and/or target mediated drug disposition, which is expected for an IgG-based antibody. The data provided suggest similar PK (Cl as well as half life) in UC patients compared with RA patients and healthy subjects.

The MAH has provided an analysis of golimumab dose linearity/proportionality in UC patients based on observed plasma concentration vs. time data. Looking at the IV data, there are some signs of disproportional increase in concentration in the range from 1 mg/kg to 4 mg/kg for IV administration (at Week 6 after start of administration). For the SC data there is a similar trend at week 6 after start of administration, albeit more subtle. The MAH speculated that this may be due to target mediated drug disposition as expected for a monoclonal antibody. Looking at the totality of data and taking the rather limited deviation from proportionality into account it is fair to conclude that pharmacokinetics of golimumab is approximately dose-proportional following SC administration over a dose range of 50 mg to 400 mg.

Following induction doses of 200 mg and 100 mg golimumab at week 0 and 2, respectively, and maintenance doses of 50 mg or 100 mg golimumab subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 μg/ml and 1.8 ± 1.1 μg/ml, respectively. In UC patients treated with 50 mg or 100 mg golimumab subcutaneously every 4 weeks, concomitant use of immunomodulators did not have a substantial effect on steady-state trough levels of golimumab.

2.3.5. Conclusions on clinical pharmacology

Since golimumab is an IgG-based antibody directed towards TNF-alpha, target mediated drug disposition is expected. The data provided from both from healthy subjects and UC patients suggested a slightly more than dose-proportional increase in golimumab exposure. The PK in patients with UC does not seem to differ substantially from that in patients with RA and healthy subjects. This is an expected result, golimumab being an antibody and the parenteral administration should make the uptake independent of gastrointestinal disease.

The proposed dose regimen with a higher initial dose followed by a second dose after 2 weeks before starting the maintenance monthly dosing seems reasonable from a pharmacokinetic perspective, reaching therapeutic plasma levels rapidly.

2.4. Clinical efficacy

The assessment of efficacy in the sought indication was based on the randomised Phase II/III induction study C0524T17 and 54-week data of the phase III maintenance study C0524T18. An extension of study C0524T18 is ongoing. The study extension began at Week 54 and is to continue through Week 228.

2.4.1. Dose response study

Induction study C0524T17 was divided in two parts: part 1 was a phase II dose-ranging portion and part 2 was a phase III dose-confirming portion. In the part 1 of the respective study, several doses were evaluated for continuation in part 2. On completion of part 1 data were analysed and the doses for part 2 were chosen.

Study C0524T17

The subcutaneous (SC) induction doses were based on results of infliximab studies in inflammatory bowel disease (IBD), predictions of previous and ongoing studies of golimumab and from preclinical studies.

The three evaluated doses were:

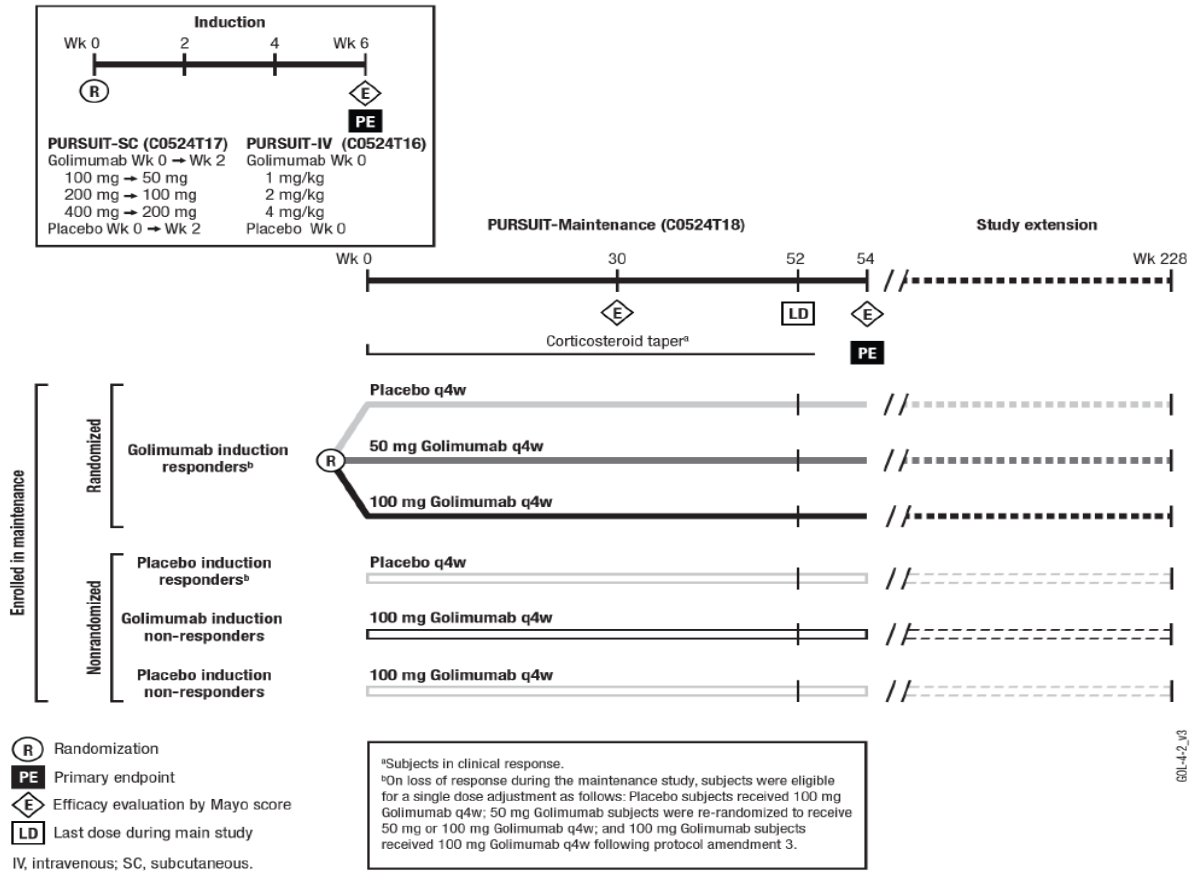
- 100 mg at Week 0 and 50 mg at Week 2 (100 mg → 50 mg)
- 200 mg at Week 0 and 100 mg at Week 2 (200 mg → 100 mg)
- 400 mg at Week 0 and 200 mg at Week 2 (400 mg → 200 mg)

For continuation into part 2, the 200 mg → 100 mg and 400 mg → 200 mg golimumab SC dosage regimens were selected. The decision was based on PK, efficacy, exposure-response and the safety profile. Both doses were concluded to be effective and safe in the induction of clinical response.

2.4.2. Main studies

The assessment of efficacy in the sought indication was based on the randomised Phase II/III induction study C0524T17 and the phase III maintenance study C0524T18.

Figure 5. Golimumab UC Program



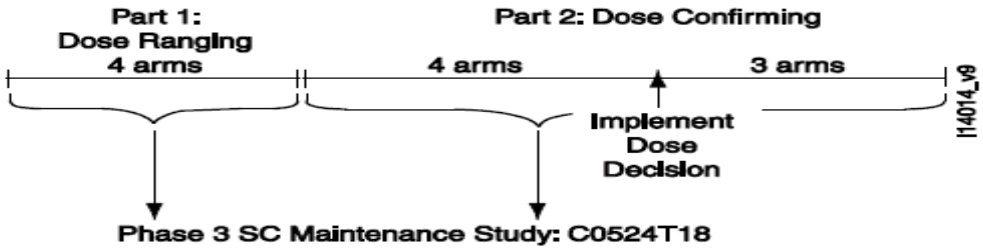
Study C0524T17: A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis (PURSUIT-Induction).

Methods

The two parts of the study, part 1 dose-finding and part 2 dose-confirming, were randomized, double-blind, placebo-controlled and of parallel-group designs. There was no break in enrolment between Part 1 and Part 2. In part 1 of the study 169 patients were randomized at Week 0. Part 2 of the study began when the 170th patient was randomized and 896 patients were randomized at Week 0 in Part 2.

At week 6, patients were evaluated for clinical response. At this visit all patients, regardless of the part of the study into which they were enrolled, were eligible to enrol in the golimumab maintenance study (C0524T18). Patients not entering the golimumab maintenance study were evaluated for safety 16 weeks following their last administration of study agent.

Figure 6. Design of study C0524T17



Study participants

Main inclusion criteria:

Subjects had to be men or women 18 years of age or older with moderately to severely active UC as defined by a Mayo score of 6 to 12 inclusive at baseline (Week 0), including an endoscopic subscore of ≥2. Subjects must have had a biopsy result consistent with the diagnosis of UC and must have been ambulatory (i.e., not at imminent risk of colectomy). Subjects must have demonstrated an inadequate response to or have failed to tolerate oral 5-aminosalicylates (5-ASAs), or oral corticosteroids, or the immunomodulators azathioprine (AZA) or 6-mercaptopurine (6 MP), or have demonstrated corticosteroid dependence (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC).

Main exclusion criteria

Subjects were not to be enrolled into the study if they were at imminent risk of colectomy. Subjects with UC limited to the rectum only or <20 cm of the colon, a stoma, a fistula, an obstruction, or adenomatous colonic polyps that were not removed were ineligible for entry into the study. Subjects with a history of latent or active granulomatous infection (including TB), a predisposition to infections, or a history of or increased potential for malignancy were ineligible for entry into the study. Subjects with a diagnosis or history of congestive heart failure, lymphoproliferative disease, systemic lupus erythematosus, or demyelinating disease were ineligible for entry into the study. Subjects with prior exposure to biologic anti-TNF agents were ineligible for entry into the study.

Treatments

Patients in part 1 were randomized in a 1:1:1:1 ratio to one of the following dose regimens:

- placebo at Week 0 and placebo at Week 2 (placebo)
- golimumab 100 mg at Week 0 and 50 mg at Week 2 (100 mg → 50 mg)
- golimumab 200 mg at Week 0 and 100 mg at Week 2 (200 mg → 100 mg)
- golimumab 400 mg at Week 0 and 200 mg at Week 2 (400 mg → 200 mg)

While the data from Part 1 were being evaluated, newly enrolled subjects in Part 2 were equally randomised to the same SC doses of golimumab or placebo as in Part 1. After the interim analysis, the selected doses were the 200 mg → 100 mg and 400 mg → 200 mg golimumab SC dose regimens for continued development in Part 2. Newly enrolled patients in Part 2 were thereafter equally randomized to 200 mg →100 mg or 400 mg → 200 mg golimumab or placebo.

Objectives

The primary objectives of part 1 of the study were to evaluate dose response and to select a SC induction regimen for golimumab.

Objectives of the second part were to evaluate the efficacy and safety of golimumab in inducing clinical response.

Outcomes/endpoints

The primary endpoint was clinical response at week 6 defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

The major secondary endpoints evaluated at week 6 were:

- Clinical remission (Mayo score ≤2 with no individual subscore >1)
- Mucosal healing (endoscopy subscore 0 or 1)
- Change from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) score (a ≥20 point improvement was considered to be consistent with response)

Sample size

It was estimated that 176 patients in total would provide ≥80% probability of detecting a dose-response relationship in part 1 of the study.

The sample size for Part 2 was based on the consideration of statistical power and the objective to provide the target study population to be evaluated in the golimumab maintenance study C0524T18.

Since no data were available for golimumab in the treatment of UC, estimates used for the sample size calculation were obtained from the ACT 1 and ACT 2 studies of infliximab in subjects with moderately to severely active UC.

Due to the termination of the C0524T16 study the sample size of part 2 of study C0524T17 was increased to provide a sufficient number of subjects to enrol in and adequately power study C0524T18.

Randomisation

An IVRS was used to randomly assign subjects to study treatment and dispense study agent. In Part 1, subjects were randomly assigned to receive placebo or 1 of 3 dose regimens of golimumab (100 mg → 50 mg, 200 mg → 100 mg, or 400 mg → 200 mg at Week 0 and 2, respectively) using an adaptive randomization procedure, with investigative site as the stratification variable. The randomization

method was a minimization procedure with a biased-coin assignment. In Part 2, eligible subjects were allocated to a treatment regimen using a permuted block randomization.

Blinding (masking)

There were no visual differences in appearance between the syringes of placebo and golimumab. The designated pharmacists or other appropriately licensed and authorized personnel who dispensed the study agent and independent drug monitors were unblinded to study agent. The subjects, site monitors, principal investigator and all the investigator site staff were blinded to study agent assignment. To protect the integrity of the study and the golimumab maintenance study C0524T18, treatment assignment blinding was maintained for investigative sites, site monitors and subjects participating in this study until the Week 54 analyses for the maintenance study were completed. Sponsor personnel were unblinded to treatment assignment for this study in 2 stages. At the first database lock, the data for subjects in Part 1 were unblinded and released to a limited number of sponsor personnel for analysis; the data for all subjects in Part 2 remained blinded at this time. At the second database lock, the data for all subjects was unblinded and released to a limited number of sponsor personnel for analysis.

Statistical methods

Demographic and baseline disease characteristics were summarized for all randomized subjects. Chi-square tests or Cochran-Mantel-Haenszel [CMH] chi square tests, as appropriate, were used to compare the proportions of subjects achieving selected endpoints (e.g., clinical remission). In cases of rare events, Fisher's exact test was used for treatment comparisons.

Continuous response parameters were compared using an analysis of variance (ANOVA) or an ANOVA on the van der Waerden normal scores, as appropriate. All statistical testing was performed at the $\alpha = 0.05$ (2-sided) level unless otherwise specified.

Control of Type I error

In the C0524T17 study, after all patients in Part 1 had either completed the Week 6 visit or had terminated the study prior to Week 6, an analysis of the Part 1 data was performed to select induction doses for continued development in Part 2 of the study. No patients from Part 2 were unblinded at the time of the Part 1 database lock and the patients in Part 1 were not included in the primary analysis population, which was based on patients randomized in Part 2 after the dose selection.

In addition, due to the stopping of the C0524T16 induction study, which together with the C0524T17 induction study was to provide the required number of patients to power the maintenance study C0524T18, the number of patients in the C0524T17 study was increased. No data from patients in the primary analysis population in C0524T17 were used to determine the increase in sample size.

Since no comparisons (blinded or unblinded) of the C0524T17 data for the primary analysis population were performed prior to the final database lock, no adjustments were made to the overall Type 1 error rate ($\alpha = 0.05$, 2-sided) for the primary and major secondary endpoint analyses in the C0524T17 study.

Handling of Dropouts or Missing Data

Patients with missing observations, unless otherwise specified, the last observation was carried forward for continuous endpoints with the exception of the Mayo and partial Mayo scores, where the last available Mayo subscores were carried forward. Patients with missing data were considered as not achieving the respective endpoints for dichotomous endpoints.

Results

Participant flow

Table 2. Number of patients who terminated study participation prior to Week 6 by reason for termination; randomized patients (study C0524T17)

		Golimumab					
	Placebo	100 mg → 50 mg	200 mg → 100 mg	400 mg → 200 mg	Combined	All Golimumab	Total
Subjects randomized	331	72	331	331	662	734	1065
Subjects who terminated study participation	13 (3.9%)	6 (8.3%)	7 (2.1%)	9 (2.7%)	16 (2.4%)	22 (3.0%)	35 (3.3%)
Reason for termination							
Withdrawal of consent	4 (1.2%)	2 (2.8%)	2 (0.6%)	3 (0.9%)	5 (0.8%)	7 (1.0%)	11 (1.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)	1 (0.1%)	1 (0.1%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	9 (2.7%)	4 (5.6%)	5 (1.5%)	5 (1.5%)	10 (1.5%)	14 (1.9%)	23 (2.2%)

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There were 16 (1.5 %) patients that terminated the study drug between weeks 0 and 6. Six of the 16 patients completed the safety visit 16 weeks after the drug administration. Major reasons for terminating the study drug was AEs (placebo n=3, golimumab n=4) and lack of efficacy (n=2).

A total of 50 patients terminated study participation. Thirty-five (3.3%; including 1 patient who was randomized but never treated) terminated prior to week 6, and 15 (1.4%) terminated between week 6 and week 16.

Recruitment

The study was initiated on 18 July 2007 and completed on 29 November 2010.

Conduct of the study

There were two amendments to the protocol
Amendment 1: 08 May 2008
Amendment 2: 20 August 2009

There were 3 major changes in the first amendment that concerned:

- change to a permuted block randomization
- inclusion of corticosteroid dependant patients
- inclusion of patients refractory to or intolerant of oral 5-ASA only in order to permit for evaluation of early intervention with an anti-TNF-α agent

Major changes in the second amendment concerned:

- increase of numbers of patients in part 2 to compensate for early termination of study C0524T16
- primary analysis population was changed to include only patients that randomized to part 2 after dose selection

Baseline data

The baseline data are summarised in table 4 (see study C0524T18).

Numbers analysed

The primary analysis population was composed of patients randomized in Part 2 after the dose selection. Data from two sites (data from 13 randomized patients) were excluded from the primary efficacy analyses due to misconduct. The following pre-specified analysis populations were also evaluated for selected, pre-specified efficacy endpoints:

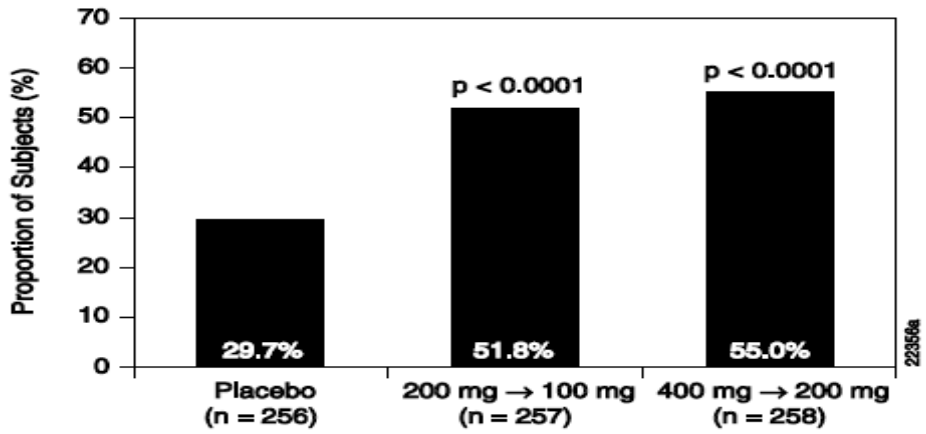
- Subjects randomized in Part 1
- Subjects randomized in Part 2
- Subjects randomized in Part 2 before the dose selection
- First 450 subjects randomized in Part 2 after the dose selection
- All randomized subjects (Part 1 and Part 2 combined)

Therefore the primary analysis population consisted of 761 subjects.

Outcomes and estimation

Primary efficacy endpoint

Figure 7. Proportions of patients in clinical response at Week 6 in C0524T17; randomized patients in Part 2 after the dose selection



The result of the primary analysis was generally consistent in subgroups (demographic, UC disease, baseline medication), in sensitivity analysis regarding missing data and exclusion of patients and in the pre-specified efficacy populations with one exception; for patients randomized in part 2 before the dose selection the effect of golimumab was not evident due to a high placebo response rate (50%).

Secondary efficacy endpoints

Table 3. Major secondary endpoints in C0524T17; randomized patients in part 2 after dose the dose selection

		Golimumab		
	Placebo	200 mg → 100 mg	400 mg → 200 mg	Combined
Randomized subjects in Part 2 after the dose selection (excluding site 7257)	256	257	258	515
Subjects in clinical remission at Week 6[a,b]	16 (6.3%)	48 (18.7%)	46 (17.8%)	94 (18.3%)
p-value		< 0.0001	< 0.0001	< 0.0001
Subjects with mucosal healing at Week 6[a, b]	73 (28.5%)	111 (43.2%)	117 (45.3%)	228 (44.3%)
p-value		0.0005	< 0.0001	< 0.0001
Change from baseline in IBDQ score at Week 6[a, b]				
n	255	256	256	512
Mean ± SD	14.6 ± 31.37	27.4 ± 33.68	27.0 ± 34.23	27.2 ± 33.92
p-value		< 0.0001	< 0.0001	< 0.0001

[a] Subjects who had a prohibited change in concomitant UC medication, an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect prior to the Week 6 visit are considered not to be in clinical remission and not to have mucosal healing, and for the IBDQ score, their baseline value was carried forward to Week 6.

[b] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical remission; subjects who had a missing endoscopy subscore at Week 6 are considered not to have mucosal healing; and subjects who had a missing IBDQ score at Week 6 had the last available value carried forward to Week 6.

Extracted from RE311:[E_CREM_1_B_BB], 27JAN2011 15:46; RE311:[E_MUCO_2_B_BB], 27JAN2011 15:46; and RE311:[E_IBDQ_1_B_BB], 27JAN2011 15:46

Results from subgroup analyses and for remaining secondary endpoints were in general supportive.

Study C0524T18: A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis (PURSUIT-Maintenance).

Methods

The Study, C0524T18, was randomized, placebo-controlled, double-blind, 3-arm, parallel-group study of the safety and efficacy of SC administration of golimumab in maintaining clinical response. Patients in clinical response to golimumab in one of the induction studies, C0524T16 or C0524T17 were invited to participate. Patients who were not in clinical response to golimumab or placebo in the induction studies were also eligible to enrol in this study but were not included in the key efficacy analyses. They were included in the safety and PK analyses only.

Patients were to be discontinued from the study drug if there was no improvement of their disease activity by week 16. For patients that lost response through week 52 the following applied:

- Placebo: Received golimumab 100 mg q4w
- Golimumab 50 mg: Re-randomized to receive golimumab 50 mg or 100 mg q4w
- Golimumab 100 mg:

1. Prior to the implementation of Protocol Amendment 3, patients were re-randomized to receive golimumab 100 mg or 200 mg q4w.

2. After the implementation of Protocol Amendment 3, patients only received golimumab 100 mg q4w. Patients who had been re-randomized to 200 mg q4w prior to implementation of Protocol Amendment 3 had their dose decreased to 100 mg q4w.

Patients on immunomodulators and oral 5-ASA at baseline should remain on the same dose regimen throughout week 54. Patients in clinical response receiving oral corticosteroids were to begin tapering the daily dose at baseline.

Patients were assessed for UC disease activity using the Mayo score at week 30 and 54 and by partial Mayo score every 4 weeks. At week 54, patients were evaluated for efficacy and safety. Patients that had successfully completed treatment (through week 52) were eligible to participate in a study extension. Patients who discontinued study agent but continued to participate in the study or did not enter the study extension were followed for 16 weeks after the last administration of study agent. Patients that discontinued prior to week 54 were followed for 54 weeks after the week 0 visit for information related to colectomy.

Study participants

The study population was adult patients with moderately to severely active UC (i.e., a Mayo score of 6 to 12, inclusive, at baseline [Week 0 of an induction study], including an endoscopic subscore of ≥ 2) who had an inadequate response to or failed to tolerate oral 5-ASAs, or oral corticosteroids, or the immunomodulators AZA or 6-MP, or had demonstrated corticosteroid dependence (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC). All patients were naive to anti-TNF therapy.

Maintenance therapy was evaluated in patients who were in clinical response to golimumab at Week 6 in either of the induction studies, C0524T16 or C0524T17.

Main inclusion criteria:

- Prior to the screening endoscopy or the earliest entry in the Mayo diary card was to be used to calculate the baseline Mayo score, whichever of these 2 events came first, the following conditions must be met:

a. If receiving 6-MP, AZA, or MTX, must have been receiving it for at least 12 weeks. The class of agent (6-MP/AZA versus MTX) prescribed may not have changed during those 12 weeks, and the dose must be stable for at least 4 weeks.
b. If 6-MP, AZA, or MTX have been recently discontinued, they must have been stopped for at least 4 weeks.
c. If receiving oral 5-ASA compounds or oral corticosteroids (including budesonide), the dose must have been stable for at least 2 weeks.
d. If oral 5-ASA compounds or oral corticosteroids (including budesonide) have been recently discontinued, they must have been stopped for at least 2 weeks.
e. The following medications/therapies must have been discontinued for at least 2 weeks:

- rectal corticosteroids (ie, corticosteroids [including budesonide] administered to the rectum or sigmoid colon via foam or enema or suppository)
- rectal 5-ASA compounds (ie, 5-ASAs administered to the rectum or sigmoid colon via foam or enema or suppository)
- parenteral corticosteroids
- total parenteral nutrition (TPN)
- pentoxifylline

- thalidomide or related agents
- antibiotics for the treatment of UC (ie, ciprofloxacin, metronidazole, or rifaximin)

f. 6-thioguanine (6-TG) must have been discontinued for at least 4 weeks.

- Must have results from a biopsy collected at the screening endoscopy procedure or have a previous biopsy result obtained within the last year that is consistent with the diagnosis of UC.

- All subjects ≥45 years of age must either have had a colonoscopy to assess for the presence of adenomatous polyps within 5 years of the first administration of study agent or a colonoscopy to assess for the presence of adenomatous polyps at the screening visit. The adenomatous polyps must be removed prior to the first administration of study agent.

All the cases of colon polyps reported in the UC trials were confirmed to be inflammatory and with no dysplasia.

Main exclusion criteria

1. Have severe extensive colitis as evidenced by:
    - Investigator judgment that the subject is likely to require a colectomy within 12 weeks of baseline.

or

- Symptom complex at screening or baseline visits that includes at least 4 of the following:
    1) diarrhoea with ≥6 bowel movements/day with macroscopic blood in stool
    2) focal severe or rebound abdominal tenderness
    3) persistent fever (≥37.5°C)
    4) tachycardia (>90 beats/minute)
    5) anemia (hemoglobin <8.5 g/dL)

2. Have UC limited to the rectum only or to <20 cm of the colon.
3. Presence of a stoma.
4. Presence or history of a fistula.
5. Require, or required within the 2 months prior to screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from study agent treatment.
6. Presence of symptomatic colonic or small bowel obstruction, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).
7. History of extensive colonic resection (e.g., less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of study agent on clinical disease activity.
8. History of colonic mucosal dysplasia. For subjects with a pathology finding of “indefinite dysplasia with reactive atypia,” the investigator should discuss the case with the medical monitor to determine eligibility.
9. Presence on screening endoscopy of adenomatous colonic polyps, if not removed prior to study entry, or history of adenomatous colonic polyps that were not removed.

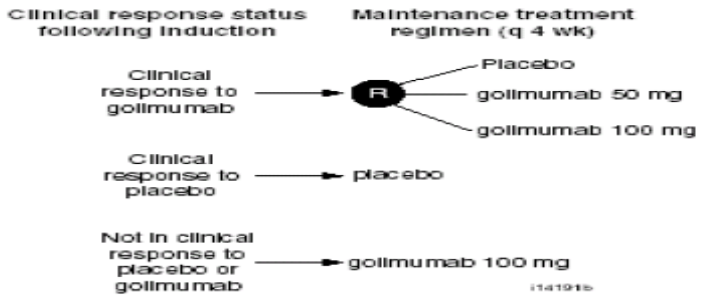
Treatments

Patients in clinical response were randomized in a 1:1:1 ratio at week 0 to receive one of the following regimens:

- placebo
- golimumab 50 mg
- golimumab 100 mg

every 4 weeks (q4w) through week 52.

Figure 8. Treatment groups in Study C0524T18



Objectives

The primary objectives were to evaluate the efficacy and safety of golimumab in maintaining clinical response.

Outcomes / endpoints

The primary endpoint was clinical response (continuous) through week 54. Clinical response is defined as a decrease from Week 0 of C0524T16 or C0524T17 in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1). Subjects who lost clinical response at any time prior to Week 54 were considered not to be in clinical response for the primary endpoint analysis.

The major secondary endpoints were:

- Clinical remission (defined as a Mayo score ≤ 2 points, with no individual subscore >1) at both week 30 and 54
- Mucosal healing (defined as endoscopy subscore of 0 or 1) at both week 30 and 54
- Clinical remission at both week 30 and 54 among subjects who were in clinical remission at week 0 of the maintenance study
- Clinical remission and not receiving corticosteroids at week 54 among subjects who were receiving corticosteroids at week 0 of the maintenance study

Sample size

The number of patients enrolled was dependant on the number who entered the study from the induction studies C0524T16 and C0524T17. The number of patients in the primary analysis population depended on the number of patients in clinical response to golimumab in the induction studies who consented to participate in this maintenance study. In order to ensure that there would be enough patients from the induction studies to meet the required number of patients for the primary analysis population of this study, at a designated time point near the completion of planned enrolment of C0524T17, the IVRS system projected, based on the available data and a predefined algorithm, whether or not the target number of patients for the primary analysis population of this study would be reached, and, if not, how many more patients from C0524T17 would need to be enrolled to reach the target. If the information provided by the IVRS vendor indicated that more patients would have been needed in this study, the sponsor may have increased the number of patients in C0524T17. Only data from this study (C0524T18) that was included in this calculation was the number of patients who had already entered the target population in this study. These data were only available to the IVRS vendor

and no sponsor personnel had access. No comparisons (blinded or unblinded) of the C0524T18 data were performed prior to the Week 54 database lock.

Randomisation

An interactive voice response system (IVRS) was used to assign patients to study treatment and dispense study agent. Patients in clinical response to golimumab at Week 6 in C0524T16 or C0524T17 were randomized in a 1:1:1 ratio at Week 0 to one of three treatment groups (placebo, golimumab 50 mg, or golimumab 100 mg) using an adaptive randomization procedure.

Stratification was performed for investigative site, clinical remission status at Week 0 (yes or no), week 0 corticosteroid use (yes or no) and mode and dose of induction dose.

Blinding (masking)

There were no visual differences in appearance between the syringes of placebo and golimumab. The designated pharmacists, or other appropriately licensed and authorized personnel who dispensed the study agent, and independent drug monitors were unblinded to study agent. The patients, site monitors, principal investigator, and all the investigator site staff were blinded to study agent assignment.

Sponsor personnel remained blinded to treatment assignments until after the week 54 database lock. The study blind was maintained for the investigative sites, site monitors, and patients until the week 54 analyses were completed.

Statistical methods

Demographic and baseline disease characteristics were summarized for all randomized subjects. Chi-square tests or Cochran-Mantel-Haenszel [CMH] chi square tests, as appropriate, were used to compare the proportions of subjects achieving selected endpoints (e.g., clinical remission). In cases of rare events, Fisher's exact test was used for treatment comparisons.

Continuous response parameters were compared using an analysis of variance (ANOVA) or an ANOVA on the van der Waerden normal scores, as appropriate. All statistical testing was performed at the $\alpha = 0.05$ (2-sided) level unless otherwise specified.

Control of Type I error

No comparisons of the C0524T18 data were performed prior to the Week 54 database lock for C0524T18, and therefore no adjustments to the overall Type 1 error rate were necessary for C0524T18.

Handling of Dropouts or Missing Data

Patients with missing observations, unless otherwise specified, the last observation was carried forward for continuous endpoints with the exception of the Mayo and partial Mayo scores, where the last available Mayo subscores were carried forward. Patients with missing data were considered as not achieving the respective endpoints for dichotomous endpoints.

Results

Participant flow

Table 4. Number of patients who discontinued study agent prior to Week 52 by reason for discontinuation; enrolled patients (study C0524T18)

	Randomized Subjects					Nonrandomized Subjects			
		Golimumab					Golimumab 100 mg		
	Placebo[a]	50 mg	100 mg	Combined	Total	Placebo[b]	Placebo Nonresponders (Induction)	Golimumab Nonresponders (Induction)	Total
Subjects enrolled	156	154	154	308	464	129	230	405	1228
Subjects who discontinued study agent	43 (27.6%)	43 (27.9%)	45 (29.2%)	88 (28.6%)	131 (28.2%)	41 (31.8%)	103 (44.8%)	216 (53.3%)	491 (40.0%)
Reason for discontinuation									
Adverse event	17 (10.9%)	12 (7.8%)	12 (7.8%)	24 (7.8%)	41 (8.8%)	12 (9.3%)	30 (13.0%)	50 (12.3%)	133 (10.8%)
Unsatisfactory therapeutic effect	19 (12.2%)	17 (11.0%)	22 (14.3%)	39 (12.7%)	58 (12.5%)	18 (14.0%)	56 (24.3%)	124 (30.6%)	256 (20.8%)
Lost to follow-up	1 (0.6%)	2 (1.3%)	1 (0.6%)	3 (1.0%)	4 (0.9%)	0 (0.0%)	3 (1.3%)	7 (1.7%)	14 (1.1%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Other	6 (3.8%)	12 (7.8%)	10 (6.5%)	22 (7.1%)	28 (6.0%)	11 (8.5%)	14 (6.1%)	34 (8.4%)	87 (7.1%)

[a] Subjects who were in clinical response to golimumab induction dosing and were randomized to placebo on entry into this maintenance study.
[b] Subjects who were in clinical response to placebo induction dosing and received placebo on entry into this maintenance study.

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Recruitment

The study was conducted at 251 study centres. The study was initiated on 28 September 2007 and completed on 24 October 2011.

Conduct of the study

There were 3 amendments to the protocol
There were 2 major changes in the first amendment:

- prohibition of 6-thioguanine (6-TG) as a concomitant medication for safety reasons
- addition of the induction dose factor as a stratum variable in the analysis of the primary endpoint

Amendment 2 concerned the following major changes:

- clarification of the re-randomization procedure on loss of clinical response where eligible patients received either the original dose or the double original dose
- patients with insufficient data (Mayo score) at week 30 or 54 should be considered not to be in clinical response for the primary endpoint analysis
- addition of the process for gauging the enrolment of subjects into the primary analysis population. A process was added to determine whether the number of subjects in C0524T17 should be increased to ensure the required number of subjects for the primary analysis population for this study.

The purpose of amendment 3 was to stop dose adjustment to golimumab 200 mg q4w after reports of lymphoproliferative cancers in subjects with long standing RA.

Baseline data

- **Baseline data**

The baseline demographic data is presented in Table 5.

Table 5. Summary of demographic characteristics, UC disease characteristics, UC concomitant medications and UC medication history at Week 0 of an induction study; randomized patients (studies T16, T17 and T18)

	Induction		Maintenance
	C0524T16	C0524T17 (after dose selection)	C0524T18[a]
Randomized subjects	291	774	464
Demographic characteristics			
Sex			
Male	59.8%	56.0%	51.9%
Female	40.2%	44.0%	48.1%
Race			
Caucasian	82.1%	82.1%	87.3%
Black	1.4%	2.5%	1.7%
Asian	15.1%	11.8%	8.2%
Other	1.4%	3.6%	2.8%
Median age (years)	40.0	38.0	39.0
Median weight (kg)	70.0	72.0	72.0
UC disease characteristics			
Median UC disease duration (years)	4.57	4.30	4.55
Median Mayo score	8.0	8.0	8.0
Extensive disease	44.7%	42.4%	44.2%
Median CRP (mg/L)	4.62	4.76	3.61
Subjects receiving concomitant UC therapies	94.2%	92.1%	93.8%
Corticosteroids (excluding budesonide)	53.3%	43.2%	51.5%
≥ 20 mg/day P.Eq	36.1%	25.1%	35.8%
Immunomodulatory drugs	31.3%	29.8%	31.7%
6-MP/AZA	30.2%	28.3%	31.0%
MTX	1.0%	1.6%	0.6%
5-ASA	81.8%	81.4%	80.2%
Subjects with inadequate response, intolerance, or dependence on conventional UC therapy	99.3%	100.0%	100.0%
Refractory to, dependent on, or intolerant of corticosteroids	79.4%	68.9%	75.4%
Refractory to or intolerant of 6-MP/AZA	52.6%	49.6%	50.4%
Refractory to or intolerant of 5-ASAs[b]	94.6%	95.7%	94.5%

5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; AZA = azathioprine; MTX = methotrexate; P.Eq = prednisone equivalent;
[a]Randomized subjects who were golimumab induction responders
[b]These data were only collected for subjects recruited following implementation of Protocol Amendment 1 of the induction studies.

Extracted from: RE309:[P_IBD_16_A_CC], 23NOV2011 10:42; RE311:[P_IBD_12_B_BB], 08DEC2010 16:13; RE310:[P_IBD_12_B], 29OCT2009 17:22; RE310:[P_MEDS_5_A], 29OCT2009 17:23; RE310:[P_MEDS_24_A], 17MAR2010 16:51; RE311:[P_MEDS_5_B_BB], 08DEC2010 16:20; RE311:[P_MEDS_146_B_BB], 08DEC2010 16:21; RE309:[P_MEDS_176_A_CC], 23NOV2011 10:45; RE309:[P_MEDS_146_B_CC], 23NOV2011 10:45; RE310:[P_DEM_1_B], 29OCT2009 17:22; RE311:[P_DEM_1_D_DD], 08DEC2010 16:36; RE309:[P_DEM_49_A_CC], 29NOV2011 17:35; RE599:[P_MEDS_146_A], 19APR2012 14:25

Table 6. Summary of UC disease characteristics at Week 0 of an induction study; enrolled subjects (study C0524T18)

	Randomized Subjects					Nonrandomized Subjects			
		Golimumab					Golimumab 100 mg		
	Placebo[a]	50 mg	100 mg	Combined	Total	Placebo[b]	Placebo Nonresponders (Induction)	Golimumab Nonresponders (Induction)	Total
Subjects enrolled	156	154	154	308	464	129	230	405	1228
UC disease duration (yrs)									
n	156	154	154	308	464	129	230	405	1228
Mean ± SD	6.89 ± 6.956	6.82 ± 6.926	7.18 ± 7.038	7.00 ± 6.973	6.96 ± 6.960	6.27 ± 7.022	6.18 ± 6.395	6.14 ± 5.936	6.47 ± 6.543
Median	4.18	4.50	4.79	4.60	4.55	3.83	4.27	4.33	4.32
IQ range	(1.89, 9.73)	(2.20, 8.85)	(2.67, 10.02)	(2.44, 9.63)	(2.20, 9.73)	(1.97, 8.17)	(1.97, 8.16)	(1.81, 8.60)	(2.01, 8.88)
Range	(0.1, 36.9)	(0.1, 37.7)	(0.1, 41.7)	(0.1, 41.7)	(0.1, 41.7)	(0.2, 48.3)	(0.1, 43.4)	(0.1, 34.4)	(0.1, 48.3)
p-value					0.894				
Extent of disease									
n	156	154	154	308	464	129	229	405	1227
Limited to left side of colon	86 (55.1%)	80 (51.9%)	93 (60.4%)	173 (56.2%)	259 (55.8%)	77 (59.7%)	125 (54.6%)	245 (60.5%)	706 (57.5%)
Extensive	70 (44.9%)	74 (48.1%)	61 (39.6%)	135 (43.8%)	205 (44.2%)	52 (40.3%)	104 (45.4%)	160 (39.5%)	521 (42.5%)
p-value					0.321				
Mayo score (0-12)									
n	156	154	154	308	464	129	230	405	1228
Mean ± SD	8.3 ± 1.37	8.1 ± 1.38	8.5 ± 1.34	8.3 ± 1.37	8.3 ± 1.36	8.2 ± 1.65	8.2 ± 1.42	8.6 ± 1.54	8.4 ± 1.47
Median	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
IQ range	(7.0, 9.0)	(7.0, 9.0)	(8.0, 9.0)	(7.0, 9.0)	(7.0, 9.0)	(7.0, 9.0)	(7.0, 9.0)	(7.0, 10.0)	(7.0, 9.0)
Range	(6, 12)	(6, 12)	(6, 12)	(6, 12)	(6, 12)	(6, 12)	(5, 12)	(6, 12)	(5, 12)
p-value					0.138				
Severity of UC disease									
n	156	154	154	308	464	129	229	405	1227
Moderate disease (Mayo score ≥ 6 to ≤ 10)	145 (92.9%)	145 (94.2%)	143 (92.9%)	288 (93.5%)	433 (93.3%)	116 (89.9%)	217 (94.8%)	352 (86.9%)	1118 (91.1%)
Severe disease (Mayo score > 10)	11 (7.1%)	9 (5.8%)	11 (7.1%)	20 (6.5%)	31 (6.7%)	13 (10.1%)	12 (5.2%)	53 (13.1%)	109 (8.9%)
p-value					0.878				
CRP (mg/L)									
n	150	149	152	301	451	122	225	399	1197
Mean ± SD	9.58 ± 15.482	8.52 ± 12.785	8.91 ± 14.736	8.72 ± 13.783	9.00 ± 14.359	9.45 ± 13.720	9.55 ± 14.776	13.22 ± 20.035	10.56 ± 16.574
Median	3.20	4.51	3.35	3.98	3.61	3.71	4.69	6.34	4.64
IQ range	(0.97, 10.10)	(1.59, 8.87)	(1.11, 10.90)	(1.33, 10.10)	(1.21, 10.10)	(0.96, 11.30)	(1.48, 10.90)	(2.58, 15.40)	(1.55, 12.50)
Range	(0.1, 85.8)	(0.1, 74.1)	(0.1, 98.2)	(0.1, 98.2)	(0.1, 98.2)	(0.1, 67.9)	(0.1, 102.0)	(0.1, 240.0)	(0.1, 240.0)
p-value					0.652				

[a] Subjects who were in clinical response to golimumab induction dosing and were randomized to placebo on entry into this maintenance study.
[b] Subjects who were in clinical response to placebo induction dosing and received placebo on entry into this maintenance study.

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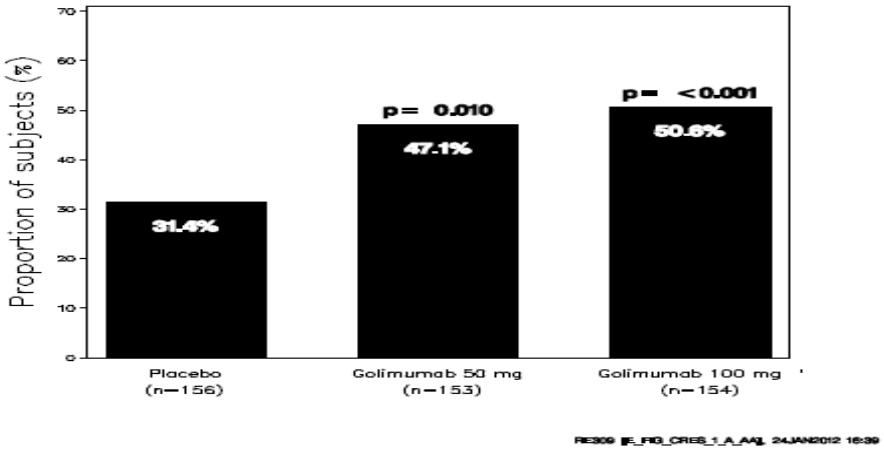
Numbers analysed

The primary analysis population is subjects randomized at Week 0 of this maintenance study (i.e., subjects in clinical response to golimumab induction at Week 0 of this maintenance study as determined by the IVRS), excluding those from 3 sites(sites 6706, 7257 and 7407). Therefore, there were 456 subjects in the primary analysis population.

Outcomes and estimation

Primary efficacy endpoint

Figure 9. Proportion of patients in clinical response through Week 54; randomized patients (study C0524T18)



In the target population, 37 % (172) patients had a dose adjustment. Dose adjustment due to loss of clinical response was the most common treatment failure criteria. The rate in the placebo group was 49% followed by 34% and 28% in the 50 mg and 100 mg groups, respectively.

Of patients in the 50 mg group that had a dose adjustment and that were re-randomized to receive the same dose, 37% (n=10) were in clinical response at week 54. The corresponding figure for patients that were randomized to receive 100 mg was 28% (n=7). Increasing the dose to 100 mg at dose adjustment did not impact clinical response or partial Mayo score. Corresponding efficacy analyses for patient in the 100 mg group who had a dose adjustment have not been performed.

The result of the primary analysis was generally consistent in subgroups (demographic, UC disease, baseline medication) and in the pre-specified sensitivity analysis regarding missing data and exclusion of patients.

Table 7. Major secondary endpoints in C0524T18; primary analysis population (study C0524T18)

	C0524T18		
		Golimumab	
	Placebo	50 mg	100 mg
Primary analysis population	156	153	154
Clinical remission at both Week 30 and Week 54	15.4%	23.5%	28.6%
p-value		0.091	0.003
Mucosal healing at both Week 30 and Week 54	26.9%	41.8%	43.5%
p-value		0.011[a]	0.001
Number of subjects in clinical remission at Week 0	54	52	57
Maintenance of clinical remission through Week 54	24.1%	36.5%	40.4%
p-value		0.365	0.073
Number of subjects on corticosteroids at Week 0	87	79	83
Clinical remission and not receiving corticosteroids at Week 54	18.4%	27.8%	22.9%
p-value		0.299	0.464

[a] Although the nominal p value for the 50 mg group versus placebo was 0.011, statistical significance for the 50 mg group could not be claimed due to the fact that the 50 mg group did not test positive for the first major secondary endpoint of clinical remission at both Week 30 and Week 54.

Extracted from: RE309:[E_CREM_1_A_AA], 23NOV2011 10:12; RE309:[E_MUCO_2_A_AA], 23NOV2011 10:13; RE309:[E_CREM_1_B_AA], 23NOV2011 10:12; RE309:[E_CREM_116_A_AA], 23NOV2011 10:13

Table 8. Summary of the Mayo score through Week 54; randomized subjects (excluding sites 6706 and 7257) (study C0524T18)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	156	153	154	307
Week 0 of an induction study				
n	156	153	154	307
Mean ± SD	8.3 ± 1.37	8.2 ± 1.38	8.5 ± 1.34	8.3 ± 1.37
Median	8.0	8.0	8.0	8.0
IQ range	(7.0, 9.0)	(7.0, 9.0)	(8.0, 9.0)	(7.0, 9.0)
Range	(6, 12)	(6, 12)	(6, 12)	(6, 12)
Week 0 of this maintenance study				
n	156	153	154	307
Mean ± SD	3.0 ± 1.82	3.1 ± 1.56	3.1 ± 1.73	3.1 ± 1.65
Median	3.0	3.0	3.0	3.0
IQ range	(2.0, 4.0)	(2.0, 4.0)	(2.0, 4.0)	(2.0, 4.0)
Range	(0, 7)	(0, 7)	(0, 7)	(0, 7)
Week 30[a,b]				
n	156	153	154	307
Mean ± SD	5.5 ± 3.43	4.3 ± 3.23	4.1 ± 3.35	4.2 ± 3.29
Median	6.0	3.0	3.0	3.0
IQ range	(2.0, 9.0)	(2.0, 7.0)	(1.0, 7.0)	(1.0, 7.0)
Range	(0, 12)	(0, 12)	(0, 12)	(0, 12)
p-value		<0.001	<0.001	<0.001
Week 54[a,b]				
n	156	153	154	307
Mean ± SD	6.0 ± 3.47	4.8 ± 3.57	4.5 ± 3.49	4.7 ± 3.53
Median	7.0	5.0	4.0	4.0
IQ range	(2.0, 9.0)	(1.0, 8.0)	(1.0, 8.0)	(1.0, 8.0)
Range	(0, 12)	(0, 12)	(0, 12)	(0, 12)
p-value		0.002	<0.001	<0.001

[a] Subjects who had a prohibited change in UC medication, an ostomy or colectomy, a dose adjustment, or discontinued study agent due to lack of therapeutic effect prior to the Week 54 visit had their Week 0 Mayo score of an induction study carried forward from the time of the event onward.
[b] Subjects who had all 4 Mayo subscores missing at a timepoint had their last available individual Mayo subscores carried forward to that timepoint.

Corticosteroid Use

At baseline, when tapering of the daily dose of corticosteroid began, the median daily dose was similar in the treatment groups. At week 30, daily doses were decreased in the 100 mg group (-7.50) and in

the 50 mg group (-10.00) while there were no change in the placebo group. At week 54 doses were similar in the 100 mg and the placebo group while there was still a decrease in the 50 mg group.

The proportions of subjects who were not receiving concomitant corticosteroids at Week 54 were greater in the 100 mg group (32.9%) and significantly greater in the 50 mg group (41.0%) compared with the placebo group (21.8%; p = 0.028).

The proportions of subjects who maintained clinical response through Week 54 and were not receiving concomitant corticosteroids at Week 54 were greater in the 100 mg group (30.5%) and significantly greater in the 50 mg group (38.5%) compared with the placebo group (20.7%; p = 0.026).

Numbers of UC related hospitalizations were low across all treatment groups.

The rate of colectomies through week 54, were 1.3% (n=2), 2.6% (n=4) and 1.9% (n=3) in the 100 mg, 50 mg and placebo groups, respectively.

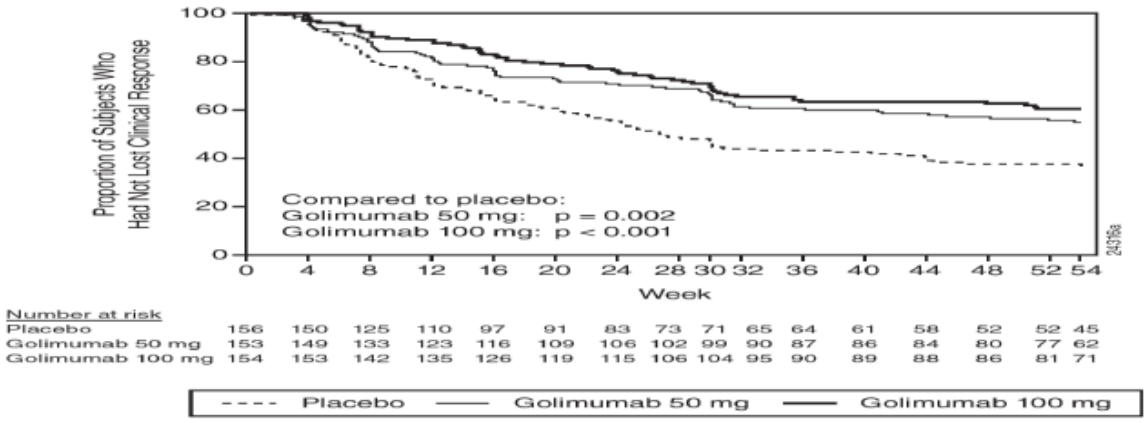
Approximately 35% of the patients in the primary analysis population were in clinical remission at week 0. The study was not powered to detect a difference between the active and placebo treatment for this endpoint.

Median CRP concentrations, faecal lactoferrin and calprotectin were lower in the 100 mg group than for patients in the placebo group and 50 mg groups at weeks 30 and 54.

Ancillary analyses

The time to first loss of clinical response through Week 54 is presented in Figure 10. The time to loss of clinical response was significantly longer in the 100 mg and 50 mg groups compared with the placebo group (p < 0.001 and p = 0.002, respectively). The median time to loss of clinical response was greater than 54 weeks in the 100 mg and 50 mg groups (i.e., more than half of the subjects had not met the criteria for loss of clinical response by Week 54) and 27 weeks in the placebo group.

Figure 10. Kaplan-Meier Curve for the time to the first occurrence of loss of clinical response through Week 54; randomized patients (study C0524T18)



In order to address the GCP issue regarding the misconduct at study site 7407, the Applicant presented the tables below to reflect the revised efficacy results for the PURSUIT – Induction and PURSUIT – Maintenance, excluding site 7407.

Table. Number of subjects in clinical response at Week 6; randomized patients in Part 2 of C0524T17 after the dose selection (excluding sites 7257 and 7407)

PURSUIT-INDUCTION				
	Placebo	**200 -> 100 mg golimumab**	**400 -> 200 mg golimumab**	**Combined golimumab**
Randomized subjects in part 2 of C0524T17 after dose selection (excluding sites 7257 and 7407)	251	253	257	510
Week 6				
n	251	253	257	510
Subjects in clinical response [a, b]	76 (30.3%)	129 (51.0%)	141 (54.9%)	270 (52.9%)
p-value		<0.0001	<0.0001	<0.0001

[a] Subjects who had a prohibited change in concomitant UC medication, an ostomy or colectomy, or discontinued study agent

due to lack of therapeutic effect prior to the Week 6 visit are considered not to be in clinical response.

[b] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical response.

Table 3. Major secondary endpoints in C0524T17; randomized patients in part 2 after dose the dose selection

		Golimumab		
	Placebo	200 mg → 100 mg	400 mg → 200 mg	Combined
Randomized subjects in Part 2 of C0524T17 after the dose selection (excluding sites 7257 and 7407)	251	253	257	510
Subjects in clinical remission at Week 6 [a,b]	16 (6.4%)	45 (17.8%)	46 (17.9%)	91 (17.8%)
p-value		< 0.0001	< 0.0001	< 0.0001
Subjects with mucosal healing at Week 6 [a,b]	72 (28.7%)	107 (42.3%)	116 (45.1%)	223 (43.7%)
p-value		0.0014	0.0001	< 0.0001

	Placebo	Golimumab 200 mg → 100 mg	Golimumab 400 mg → 200 mg	Combined
Change from baseline in IBDQ score at Week 6[a,b]				
n	250	252	255	507
Mean ±SD	14.8 ±31.25	27.0 ±33.72	26.9 ±34.28	26.9 ±33.96
p-value		< 0.0001	< 0.0001	< 0.0001

[a] Subjects who had a prohibited change in concomitant UC medication, an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect prior to the Week 6 visit are considered not to be in clinical remission and not to have mucosal healing, and for the IBDQ score, their baseline value was carried forward to Week 6.
[b] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical remission, subjects who had a missing endoscopy subscore at Week 6 are considered not to have mucosal healing; and subjects who had a missing IBDQ score at Week 6 had the last available value carried forward to Week 6.

Table. Number of subjects in clinical response through Week 54; randomized subjects in C0524T18 (excluding sites 6706, 7257 and 7407)

PURSUIT-MAINTENANCE				
	Placebo	**50 mg golimumab**	**100 mg golimumab**	**Combined golimumab**
Randomized subjects in C0524T18 (excluding sites 6706, 7257 and 7407)	154	151	151	302
Through Week 54				
n	154	151	151	302
Subjects in clinical response [a, b]	48 (31.2%)	71 (47.0%)	75 (49.7%)	146 (48.3%)
p-value		0.010	<0.001	<0.001

[a] Subjects who had a prohibited change in concomitant UC medication, an ostomy or colectomy, or discontinued study agent

due to lack of therapeutic effect prior to the Week 6 visit are considered not to be in clinical response.

[b] Subjects who had all 4 Mayo subscores missing at Week 6 are considered not to be in clinical response.

Table 7. Key Efficacy Outcomes in C0524T18; primary analysis population (study C0524T18)

		Golimumab	
	Placebo	**50 mg**	**100 mg**
Randomized subjects in C0524T18 (excluding sites 6707, 7257, and 7407)	154	151	151
Clinical remission at both Week 30 and 54 [a, b]	24 (15.6%)	35 (23.2%)	42 (27.8%)
p-value		0.122	0.004
Mucosal healing at both Week 30 and 54 [a, b]	41 (26.6%)	63 (41.7%)	64 (42.4%)
p-value		0.011[a]	0.002
Randomized subjects on concomitant corticosteroids at Week 0	87	78	82
Clinical response through Week 54 and not receiving corticosteroids at Week 54 [a, b, c]	18 (20.7%)	30 (38.5%)	25 (30.5%)
p-value		0.026	0.138

[a] Subjects who had a prohibited change in UC medication, an ostomy or colectomy, a dose adjustment, or discontinued study agent due to lack of therapeutic effect prior to the Week 54 visit are considered not to be in clinical remission / to have mucosal healing / to have achieved the clinical endpoint of clinical response and not receiving concomitant corticosteroids.

[b] Subjects who had all 4 Mayo subscores missing at Week 30 or at Week 54 are considered not to be in clinical remission / to have mucosal healing / to have achieved the clinical endpoint of clinical response and not receiving concomitant corticosteroids.

[c] Subjects who had a missing value in corticosteroid use at Week 54 had their last value carried forward / to have achieved the clinical endpoint of clinical response and not receiving concomitant corticosteroids..

Supportive studies

Study C0524T16: A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Intravenously, in Subjects with Moderately to Severely Active Ulcerative Colitis.

An interim analysis to determine the optimal IV induction doses of golimumab was conducted after all subjects in Part 1 either completed the Week 6 visit or terminated study participation prior to Week 6.

Following the subsequent dose response analysis for the golimumab SC induction study C0524T17 and a review of the totality of the data from both induction studies, it was recommended that the C0524T16 study is stopped and enrolment into the study is terminated. It was concluded that single IV administration of golimumab in subjects with moderately to severely active UC did not lead to significant improvement in disease activity.

The study was terminated after 291 patients had been randomized and there were 115 also randomized in part 2. Patients already enrolled in the study were followed per the protocol and were invited to enter the 1-year golimumab maintenance study C0524T18.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of golimumab for induction and maintenance treatment of patients with moderately to severely active ulcerative colitis has been evaluated. Patients received induction therapies that were evaluated after 6 weeks. Two induction studies were initiated with similar design but with different dosage regimen and mode of administration (IV/SC). The study using a single IV dose of golimumab was prematurely stopped since the SC induction therapy was found to have a more favourable effect on efficacy. The SC regimens that were studied further included two doses of the study drug at weeks 0 and 2, 200 mg/100 mg or 400 mg/200mg.

Patients in clinical response in the induction studies were eligible to continue into the maintenance study. The maintenance study was of double-blind placebo-controlled design and the effect of golimumab therapy, 50 mg and 100 mg every 4 weeks, was evaluated after 52 weeks.

All patients included in the studies had experienced inadequate response to conventional therapy with corticosteroids, 6-mercaptopurine (6- MP)/azathioprine (AZA), or 5-ASA or were intolerant to or had medical contraindications for such therapies. All patients were further TNF-α naïve. According to the MAH the reason for inclusion of patients being refractory to 5-ASA only was to permit for evaluation of the efficacy and safety of early intervention with an anti-TNF-α agent. Further, it was pre-specified in the protocol that the inclusion should be limited to 10%. The MAH has presented data showing that there were 19% and 17% of patients that were refractory to 5-ASA only in the induction and maintenance studies, respectively. Excluding these patients from the efficacy analyses did not have any major impact on the results.

In general, the design and the conduct of the studies seemed appropriate. However the primary efficacy endpoint for both the induction and maintenance studies was clinical response. This is not in accordance with current guidelines where induction and maintenance of remission is considered the primary efficacy parameter to be used. Patients were recruited from the induction studies for the maintenance study and were consequently in clinical response and not in remission at baseline. However, data from the subgroup of patients that were in remission at baseline of the maintenance study were also presented (third ranked secondary endpoint). Overall, the observed difference

between placebo and active treatment was slightly larger for this group (patients in clinical remission at week 0 who maintained remission also at weeks 30 and 54). For patients in clinical response at Week 0, the difference in clinical remission at both week 30 and 54 was 8% and 12% for patients receiving 50 mg and 100 mg compared to placebo. Thus, the data from this subgroup are sufficiently supporting of efficacy.

Efficacy data and additional analyses

Following induction treatment, the observed difference between golimumab and placebo in inducing clinical response was 22% and 25% for the 200 mg/100 mg and 400 mg/200 mg doses, respectively. Corresponding figures for the induction of clinical remission were 11% and 12%.

For the maintenance treatment the observed difference between active and placebo treatment for maintaining response was 16 % for the 50 mg dose and 19 % for the 100 mg. The difference between active and placebo treatment for patients in remission both at week 30 and 54 was 8 % and 12 % for the low and high dose, respectively. Corresponding data from the subgroup of patients that were in remission at baseline of the maintenance study (n=163) and maintained remission through week 54 were 12 % and 16 %. Thus, data from this subgroup further support the efficacy.

Of all randomized patients in the maintenance study 28 % discontinued the study, the major reasons being lack of efficacy (placebo 12 %, 50 and 100 mg groups, 11 and 14 %, respectively) and AEs.

The MAH proposed not to make any recommendations as regards discontinuation of therapy in patients who have responded to treatment since patients in clinical response to anti-TNF therapy are expected to have ongoing benefit from continued treatment. It is accepted that there are at present no data available to support a recommendation and the decision to continue therapy is left at the discretion of the treating specialist. Nevertheless, collection of data from clinical practice regarding treatment interruption is important and the MAH will collect additional data regarding this point in the ongoing long-term extension of the C0524T18 trial and the proposed Nordic National Register Database Study and the Spanish Registry (as detailed in the RMP).

The available data suggested that clinical response is achieved within 12 to 14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

The initially proposed dosing for patients with UC was golimumab 200 mg SC week 0, followed by 100 mg at week 2, then 100 mg every 4 weeks, thereafter. For the already approved indications the maintenance dose is 50 mg every month. The dose may be increased to 100 mg in patients >100 kg. For the approved indications the therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

The difference between the two induction doses evaluated in part 2 of study C0524T17 was modest. The MAH's proposal to recommend the lower dose is therefore supported.

Concerning the proposed dose for maintenance treatment, 100 mg every 4 week, the clinical relevance of the difference between the two doses on efficacy and the rational for the proposed dosing is less clear. The differences between the doses were limited in spite of twice as high serum golimumab concentrations for the higher dose. Similar proportions of discontinuations due to lack of efficacy across all treatment groups further questions the rational from an efficacy point of view. In response to the question regarding the clinical relevance of the difference in efficacy between the two dosing regimens 50 mg and 100 mg, the MAH pointed out that although the response rates induced by both doses were clinically and statistically significant at week 54, maintenance of remission at weeks 30 and 54 was only statistically significant for the higher dose as compared with placebo. However, although

statistically significant, the clinical relevance of a difference in remission rate between the doses of 5 % for maintained remission was questioned by the CHMP. Furthermore, in clinical guidelines it is stated that the goal of maintenance therapy in UC is to maintain steroid-free remission. Although a difference between doses of 5% is not considered clinically relevant, in this comparison the lower dose was more effective than the higher dose (steroid-free remission at week 54; placebo 18%, low dose 28% and high dose 23%). Further, in the low dose groups there were 34% of patients that required a dose adjustment as compared to 28% in the high dose group. Corresponding figures for patients experiencing flares were 52% in the low dose group and 45% in the high dose group. Again the differences between the groups are modest (7-8%) and the importance and clinical relevance of these differences is unclear.

Concerning colectomies through week 54, the numbers of patients were limited in all treatment groups, 3, 4 and 2 respectively, in the placebo, 50 mg and 100 mg groups.

To support the use of the higher 100 mg dose, exposure-response relations have been further analysed. According to the MAH there is a positive correlation between exposure and key efficacy endpoints. The CHMP considered that the reporting of the modeling was very rudimentary and made secondary review difficult to perform. Even though a positive correlation between exposure and response is likely, the model needs to be further developed and thoroughly qualified before it can be used for the purpose of prediction. In response the MAH has presented further data that support the use of the 100 mg dose for patients >80 kg. The difference between the low and high dose groups for these patients is approximately 11-12% for the presented efficacy endpoints. The Applicant further proposed that patients <80 kg in clinical response who do not achieve clinical remission might benefit from a dose increase. However, supportive data are based on a too limited number of patients to make any firm conclusions. Thus, this proposal was not agreed by the CHMP.

Those patients on 50 mg who lost response, were re-randomised to 50 or 100 mg q4w. Following re-randomisation, there was no difference in response rate (37% vs. 28%, although numbers were small), suggesting that there is no point in increasing the dose in a patient who loses response.

Data from the maintenance study implies that for patients in the 50 mg group that lost response, a dose increase did not affect the outcome at week 54.

To conclude, presented data support an additional benefit of the 100 mg dose in patients >80 kg while for patients <80 kg there seems to be no major difference in clinical response/remission between the doses.

2.4.4. Conclusions on the clinical efficacy

The results of the induction and maintenance studies for treatment of patients with moderate to severe UC with golimumab show a statistically significant effect on the primary efficacy endpoint that was supported with the result of major secondary endpoints, including remission. This overall dataset is accepted for the efficacy demonstration. The observed differences between active and placebo treatment are considered to be clinically relevant for patients with inadequate response or intolerance to conventional therapy. Based on the available data the 50 mg q4w dose is the recommended maintenance dose for patients with body weight less than 80 kg whereas patients >80 kg would benefit from a higher dose i.e. 100 mg q4w.

2.5. Clinical safety

2.5.1. Introduction

Data from the induction studies C0524T16 and C0524T17 and from the maintenance study C0524T18 contributed to the safety evaluation.

The safety presentations include:

- Summary of the safety data from the three individual UC studies.
- Pooled safety data from the three UC studies from Week 0 of induction through Week 54 of maintenance for patients randomized in C0524T18 for a total of 60 weeks of follow-up.
- Data pooled from the UC studies and other disease populations in which golimumab has been studied (events of special interest and malignancies)

Events of special interest include sepsis, pneumonia, tuberculosis (TB), opportunistic infections, cellulitis, demyelination, congestive heart failure (CHF), hypersensitivity reactions, serum sickness-like and anaphylactic reactions, and hepatobiliary events.

Study C0524T17

Two populations were evaluated for safety; all treated patients (parts 1 and 2 combined) and treated patients after dose selection in part 2. 734 patients received at least one dose of golimumab.

Study C0524T18

Three populations were evaluated, randomized patients (the target population), non-randomized patients and all treated patients through week 54. The data presentations focus on the placebo, 50 mg and 100 mg treatment groups. There were only 14 patients that received the 200 mg dose. There were 1075 patients receiving active treatment;

- 741 (69 %) were exposed for at least 6 months
- 536 (50 %) were exposed for at least one year

Data from other indications

Data from studies in other disease populations involve 3935 patients and 7534 patient-years of follow-up, and have been assessed within previous applications.

Patient exposure

The dose regimens and number of subjects evaluated in each of the UC studies are presented in Table 9.

Table 9: Golimumab clinical studies in subjects with moderately to severely active UC

Study Number\Phase	Duration of Follow-up for this Submission	Doses Administered (Treated Subjects)
C0524T16, Phase 2/3	6 weeks for subjects entering C0524T18 16 weeks following the last study agent administration for subjects not entering C0524T18	**IV administration at Week 0:** Placebo 77 1 mg/kg 63 2 mg/kg 74 4 mg/kg 76
C0524T17, Phase 2/3	6 weeks for subjects entering C0524T18 16 weeks following the last study agent administration for subjects not entering C0524T18	**SC administration at Week 0 and at Week 2:** Placebo → placebo 330 100 mg → 50 mg 71 200 mg → 100 mg 331 400 mg → 200 mg 332
C0524T18, Phase 3	54 weeks	**SC administration every 4 weeks:** **Subjects in response to golimumab induction (Randomized Subjects)** Placebo 156 50 mg 154 100 mg 154 **Other populations (Nonrandomized Subjects)** Placebo (pbo induction responders) 129 100 mg (pbo induction nonresponders) 230 100 mg (gol induction nonresponders) 405
Gol = golimumab; pbo = placebo		

For the Phase 2b and Phase 3 SC studies of RA, PsA, and AS studies, a total of 2363 subjects were treated with at least 1 dose of golimumab and had a total of 5714 subject-years of followup.

Long-term exposure for the 50 mg and 100 mg golimumab doses for the Phase 3 SC studies of RA, PsA, and AS are provided in Table 10.

Table 10. Summary of duration of golimumab exposure for phase III SC studies of RA, PsA and AS

	Golimumab 50 mg	Golimumab 100 mg
Subjects treated with golimumab in the Phase 3 SC rheumatology studies[c]	1245	1377
Duration of golimumab exposure during Phase 3 SC rheumatology studies		
At least 6 months[a]	1017 (81.7%)	1172 (85.1%)
At least 1 year[b]	826 (66.3%)	1004 (72.9%)
At least 96 weeks	358 (28.8%)	762 (55.3%)

[a] The duration between the first and last golimumab administration on the indicated dose was at least 24 weeks.
[b] The duration between the first and last golimumab administration on the indicated dose was at least 52 weeks.
c Subjects may appear in more than one column.

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Adverse events

Study C0524T16

Thirty-one (31) percent of patients in the placebo group and 36% of patients treated with golimumab had AEs. Most frequently reported AEs were in the SOC Gastrointestinal disorders with the most common being colitis ulcerative (2.6% and 3.8% in placebo and actively treated patients).

Study C0524T17

Table 11. Number of patients with 1 or more treatment-emergent adverse events (with frequency of ≥2% in any golimumab or placebo group) through Week 6 by MedDRA preferred term; treated patients

		Golimumab				
	Placebo	100 mg → 50 mg	200 mg → 100 mg	400 mg → 200 mg	Combined	All Golimumab
Subjects treated	330	71	331	332	663	734
Avg duration of follow-up (weeks)	6.05	5.95	6.08	6.09	6.09	6.07
Avg exposure (number of administrations)	1.98	1.97	1.99	1.99	1.99	1.99
Subjects with 1 or more adverse events	126 (38.2%)	34 (47.9%)	124 (37.5%)	129 (38.9%)	253 (38.2%)	287 (39.1%)
Preferred terms						
Headache	17 (5.2%)	5 (7.0%)	10 (3.0%)	15 (4.5%)	25 (3.8%)	30 (4.1%)
Nasopharyngitis	11 (3.3%)	2 (2.8%)	11 (3.3%)	8 (2.4%)	19 (2.9%)	21 (2.9%)
Pyrexia	7 (2.1%)	2 (2.8%)	6 (1.8%)	10 (3.0%)	16 (2.4%)	18 (2.5%)
Nausea	7 (2.1%)	1 (1.4%)	3 (0.9%)	12 (3.6%)	15 (2.3%)	16 (2.2%)
Anaemia	7 (2.1%)	1 (1.4%)	9 (2.7%)	5 (1.5%)	14 (2.1%)	15 (2.0%)
Colitis ulcerative	13 (3.9%)	2 (2.8%)	7 (2.1%)	6 (1.8%)	13 (2.0%)	15 (2.0%)
Injection site erythema	0 (0.0%)	3 (4.2%)	5 (1.5%)	4 (1.2%)	9 (1.4%)	12 (1.6%)
Abdominal pain	5 (1.5%)	1 (1.4%)	2 (0.6%)	8 (2.4%)	10 (1.5%)	11 (1.5%)
Arthralgia	7 (2.1%)	0 (0.0%)	3 (0.9%)	6 (1.8%)	9 (1.4%)	9 (1.2%)
Rash	5 (1.5%)	2 (2.8%)	2 (0.6%)	3 (0.9%)	5 (0.8%)	7 (1.0%)
Cough	9 (2.7%)	0 (0.0%)	3 (0.9%)	3 (0.9%)	6 (0.9%)	6 (0.8%)
Insomnia	3 (0.9%)	2 (2.8%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	4 (0.5%)
Oral herpes	1 (0.3%)	2 (2.8%)	2 (0.6%)	0 (0.0%)	2 (0.3%)	4 (0.5%)
Back pain	2 (0.6%)	2 (2.8%)	1 (0.3%)	0 (0.0%)	1 (0.2%)	3 (0.4%)

The proportion of reasonable (possibly, probably or definitely) related events was 15-17 % with no major differences between treatment groups.

The proportions of patients with AEs of severe intensity were 15.5 % and 16.8 % in the placebo and active groups, respectively.

Study C0524T18

Table 12. Number of patients with 1 or more treatment-emergent adverse events (with frequency of ≥5% in the golimumab 50 mg or the golimumab 100 mg or the placebo group) through Week 54 by MedDRA preferred term; treated patients who were randomized

		Golimumab[a]			Dose Adjustment[b]			
	Placebo[a,c]	50 mg	100 mg	Combined	Placebo → 100 mg	50 mg → 100 mg	100 mg → 200 mg[d]	All Golimumab[e]
Treated subjects who were randomized	156	154	154	308	76	25	14	384
Avg duration of follow-up (weeks)	32.7	44.3	46.3	45.3	32.1	25.9	27.5	45.4
Avg exposure (number of administrations)	8.2	11.1	11.3	11.2	7.6	5.5	6.9	11.1
Subjects with 1 or more adverse events	103 (66.0%)	112 (72.7%)	113 (73.4%)	225 (73.1%)	54 (71.1%)	16 (64.0%)	9 (64.3%)	285 (74.2%)
Preferred terms								
Colitis ulcerative	29 (18.6%)	27 (17.5%)	24 (15.6%)	51 (16.6%)	13 (17.1%)	4 (16.0%)	1 (7.1%)	69 (18.0%)
Nasopharyngitis	11 (7.1%)	14 (9.1%)	21 (13.6%)	35 (11.4%)	7 (9.2%)	4 (16.0%)	3 (21.4%)	46 (12.0%)
Headache	14 (9.0%)	12 (7.8%)	12 (7.8%)	24 (7.8%)	8 (10.5%)	2 (8.0%)	1 (7.1%)	35 (9.1%)
Arthralgia	12 (7.7%)	11 (7.1%)	8 (5.2%)	19 (6.2%)	7 (9.2%)	0 (0.0%)	1 (7.1%)	27 (7.0%)
Abdominal pain	4 (2.6%)	11 (7.1%)	11 (7.1%)	22 (7.1%)	3 (3.9%)	2 (8.0%)	0 (0.0%)	26 (6.8%)
Upper respiratory tract infection	4 (2.6%)	8 (5.2%)	9 (5.8%)	17 (5.5%)	6 (7.9%)	3 (12.0%)	1 (7.1%)	26 (6.8%)
Rash	3 (1.9%)	9 (5.8%)	7 (4.5%)	16 (5.2%)	1 (1.3%)	0 (0.0%)	1 (7.1%)	18 (4.7%)
Pharyngitis	4 (2.6%)	8 (5.2%)	5 (3.2%)	13 (4.2%)	2 (2.6%)	0 (0.0%)	1 (7.1%)	16 (4.2%)
Cough	5 (3.2%)	5 (3.2%)	9 (5.8%)	14 (4.5%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	15 (3.9%)

[a] Includes data up to the time of dose adjustment for those who increased dose.
[b] Includes data from the time of dose adjustment onward.
[c] Subjects who were in clinical response to golimumab induction dosing and were randomized to placebo on entry into this maintenance study.
[d] Includes data from the time of dose decrease for subjects who were dose adjusted to golimumab 200 mg from golimumab 100 mg and later on had their dose decreased from 200 mg to 100 mg.
[e] Includes data from the time of the first golimumab dose onward.

RE309:[S_AE_236_A_AA], 23NOV2011 10:17

The system organ class with the highest reported number of AEs were Gastrointestinal disorders and Infections and infestations.

Treatment-emergent AEs of severe intensity were reported by 8.3%, 10.4% and 14.3% in the placebo, 50 mg and 100 mg groups, respectively. Colitis ulcerative was the most commonly reported severe AE.

For randomized patients the proportion of reasonable related events were 28%, 25% and 36% in the placebo, 50 mg and 100 mg groups, respectively.

Approximately 75% of non-randomized patients reported one or more treatment related AEs. The highest proportion of AEs was Gastrointestinal disorders.

Pooled safety data from the three UC studies

For patients who received golimumab in C0524T16 and C0524T17 and who were randomized in C0524T18, the proportions of patients with an AE from Week 0 of induction until week 54 of the maintenance study was 74%, 78%, and 79% in the placebo, 50 mg, and 100 mg maintenance treatment groups, respectively, with average weeks of follow-up of 38.8, 50.4, and 52.4, respectively.

Table 13. Patients with ≥ TEAEs (with frequency > 5% in total golimumab group) between week 0 of an induction study until week 54 (treated patients in studies C0524T16, C0524T17 and Co524T18).

	Golimumab Induction				
	Placebo Maintenance[a]	50 mg Maintenance[a]	100 mg Maintenance[a]	Combined 50 mg and 100 mg Maintenance[a]	Total Golimumab[a,b]
Treated subjects in C0524T16 and C0524T17 who were randomized in C0524T18	156	154	154	308	464
Avg duration of follow-up (weeks)	38.8	50.4	52.4	51.4	47.2
Avg exposure (number of administrations)	10.0	12.9	13.1	13.0	12.0
Subjects with 1 or more adverse events	115 (73.7%)	120 (77.9%)	122 (79.2%)	242 (78.6%)	357 (76.9%)
Preferred term					
Colitis ulcerative	29 (18.6%)	27 (17.5%)	24 (15.6%)	51 (16.6%)	80 (17.2%)
Nasopharyngitis	13 (8.3%)	16 (10.4%)	22 (14.3%)	38 (12.3%)	51 (11.0%)
Headache	17 (10.9%)	14 (9.1%)	20 (13.0%)	34 (11.0%)	51 (11.0%)
Arthralgia	14 (9.0%)	12 (7.8%)	11 (7.1%)	23 (7.5%)	37 (8.0%)
Abdominal pain	5 (3.2%)	12 (7.8%)	12 (7.8%)	24 (7.8%)	29 (6.3%)
Upper respiratory tract infection	6 (3.8%)	8 (5.2%)	10 (6.5%)	18 (5.8%)	24 (5.2%)
Rash	5 (3.2%)	9 (5.8%)	10 (6.5%)	19 (6.2%)	24 (5.2%)
Cough	5 (3.2%)	7 (4.5%)	11 (7.1%)	18 (5.8%)	23 (5.0%)

[a] Includes data up to the time of dose adjustment for those who increased dose from the indicated dose during the maintenance study.
[b] Includes data from the time of the first golimumab dose onward.

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Serious adverse event / deaths / other significant events

Study C0524T16

The proportions of patients with serious adverse events (SAEs) were 2.6 % in the placebo group and 3.8 % in golimumab groups. Flares of UC were the only SAE that was reported from more than one patient (4 golimumab treated patients).

There were no deaths during the study period.

Study C0524T17

The proportions of patients that reported SAEs were 6% (n=20) in the placebo group and 3% (n=20) in the golimumab groups. The most commonly reported events were colitis ulcerative followed by anaemia, dehydration and erythema nodosum. The numbers of patients with events that were considered to be reasonably related through week 6 were 12, 10 in the placebo group and 2 in the golimumab groups.

Serious infections were reported from 1.8% and 0.5% in the placebo and golimumab groups, respectively (through week 6). Serious infection that was reported from >1 patient was pneumonia.

There were two reports of opportunistic infections through week 6 (candidiasis and CMV infection) and 2 reports after week 6 (CMV infections).

Injection-site reactions were reported from 1.5% of placebo-treated and 3.4% of actively-treated patients. The most common reactions in the actively treated groups were injection-site erythema and pruritus.

Malignancies were reported for 2 patients, carcinoma in situ and colon cancer that were identified in biopsies from one patient prior to the randomization and thyroid cancer was reported for one patient.

One report of a demyelinating disorder occurred after completion of the induction study. The SAE was reported while the patient was treated with placebo in study C0524T18 on day 160. The patient was treated with antibiotics and was asymptomatic and the lesion was resolving at a neurologic follow-up a year later.

One patient died during the induction period due to an SAE of ischiorectal abscess, two weeks after the second golimumab dose. The patient suffered from severe ischiorectal abscess and was hospitalized. Due to the severity of the disease, there was necrosis of the rectum leading to an external fistula that was surgically treated. Subsequently perforations of the colon, requiring colectomy and ileostomy developed. Following the second surgery, peritonitis and sepsis developed that led to multisystem organ failure and approximately 10 weeks after the last dose of golimumab, the patient died.

Study C0524T18

For randomized patients in the placebo, 50 mg and 100 mg treatment groups, SAEs were reported in 7.7%, 8.4% and 14.3%, respectively. The corresponding figures after taking into account the time of follow-up were 12.6, 10.4 and 17.1 SAEs per hundred patient-years. Colitis ulcerative was the most commonly reported SAE. For non-randomized patients approximately 15% reported SAEs and in this group were UC flares most commonly reported also.

Among randomized patients the SOC with the most frequently reported AE considered to be reasonably related was Infections and infestations.

Serious infections were reported from 1.9%, 3.2% and 3.2% of patients in the placebo and golimumab 50 and 100 mg groups, respectively (randomized patients). Serious infection that was reported from >1 patient was appendicitis. Among non-randomized patients, the proportion was 2.2% 3.7% in patients receiving active treatment and no SAE was reported in the placebo group. SAEs reported from > 1 patient were disseminated TB and UC.

There were 4 cases of tuberculosis (TB) reported through week 54. The patients were male, two from India and two from Poland. None of the patients had signs or symptoms of TB at baseline. However, one patient had a positive QFT-TB test result and received prophylactic treatment for latent TB on entering the induction study. Chest x-rays were read as normal in 3 of 4 patients, one patients was reported as having an abnormal result with no suspicion of TB. Two patients discontinued the study agent and one patient was treated and continued in the study. The patient with the positive QFT-TB test result received isoniazid treatment (and was compliant) but died at day 206 of disseminated TB.

There were also 4 cases of opportunistic infections through week 54 (CMV infection (n=2), candidiasis and brain abscess).

For randomized patients through week 54, there were reports of injection-site reactions in 1.9 % of patients in the placebo and 50 mg golimumab group and 7% in the 100 mg group. There were no severe and serious events reported.

One non-serious AE of Type IV hypersensitivity reaction was reported for one patient in the golimumab 100 mg group.

There were four reports of malignancies. Two patients were diagnosed after placebo induction dosing and before receiving active treatment. The remaining two cases concerned one patient with lung adenocarcinoma (patient had COPD and had been a smoker for 40 years) and one patient with breast cancer.

There were three deaths during the maintenance period. One randomized patient, died from cardiac failure on day 335. The patient had a history of thrombosis. Two non-randomized patients died of septic shock and disseminated TB on days 364 and 206, respectively.

Four additional patients died during the long-term extension period (gallbladder adenocarcinoma, biventricular heart dysfunction, sepsis, heart failure and pneumonia).

Data pooled from the UC studies and other disease populations

The incidence (per 100 subject-years of follow-up) of events of special interest (i.e., sepsis, pneumonia, TB, opportunistic infections, cellulitis, demyelination, CHF, hypersensitivity reactions, serum sickness and anaphylactic reactions) were generally similar between all treated subjects in the UC studies and that of all disease populations in which golimumab has been studied as in table 14:

Table 24. The incidence (per 100 subject-years of follow-up) of events of special interest in patients in the UC studies and that of all disease populations in which golimumab has been studied

Event (per 100 subject-years of follow-up)	Ulcerative Colitis (n = 1233)	Across Disease Populations[a] (n = 5168)
Infections of Special Interest		
Sepsis	0.56 (CI: 0.20, 1.21)	0.42 (CI: 0.29, 0.58)
Pneumonia	1.76 (CI: 1.06, 2.75)	3.03 (CI: 2.67, 3.42)
Tuberculosis	0.37 (CI: 0.10, 0.95)	0.31 (CI: 0.21, 0.46)
Opportunistic Infections	0.28 (CI: 0.06, 0.81)	0.23 (CI: 0.14, 0.36)
Cellulitis	1.48 (CI: 0.85, 2.41)	2.29 (CI: 1.98, 2.63)
Demyelination	0.09 (CI: 0.00, 0.52)	0.06 (CI: 0.02, 0.14)
Congestive Heart Failure	0.19 (CI: 0.02, 0.67)	0.15 (CI: 0.08, 0.26)
Hypersensitivity Reactions	2.13 (CI: 1.35, 3.20)	2.72 (CI: 2.38, 3.09)
Serum Sickness and Anaphylactic Reactions	0.09 (CI: 0.00, 0.52)	0.07 (CI: 0.03, 0.15)

[a]Phase 2b and Phase 3 RA, PsA, AS Studies, Phase 2b Asthma Study, Phase 1 RA and Uveitis Studies, Phase 3 RA IV Studies, UC Studies

Among all golimumab treated UC patients, the rate of malignancies was 0.46 (CI: 0.15, 1.08) per 100 patient-years of follow-up. The corresponding figure across other disease populations is 1.06 (CI: 0.86, 1.30).

In summary,

- When SAEs in C0524T18 were analysed as randomized, the overall proportions of SAEs were similar across treatment groups. In addition, in the randomized population, the proportions of subjects with colectomy were low (i.e., 1.9%, 2.6%, and 1.3% in the placebo, 50 mg, and 100 mg groups, respectively; C0524T18 54-Week CSR\Sec6.5.5.2). These analyses based on safety data assessed according to the randomized treatment groups did not identify differences in the safety of subjects in the 50 mg versus the 100 mg groups, suggesting that the safety of 50 mg and 100 mg dose regimens is comparable.
- Among all treated subjects in C0524T18, the higher proportions of subjects with SAEs in the 100 mg group were primarily attributable to the increased rate of colitis ulcerative. This was not unexpected due to the high proportion of nonresponders in this population. When SAEs of colitis ulcerative are excluded from the analysis of all treated subjects, the safety between the 50 mg and the 100 mg dose regimens was comparable.
- No Exposure-Response (E-R) relationship was observed for SAEs or serious infections with increased golimumab exposure.
- The risks of SAEs, events of special interest, and malignancies (with the exception of TB, opportunistic infection, demyelination, and lymphoma) were similar between the 50 mg dose regimen and 100 mg dose regimen across all Phase 2b and Phase 3 studies. Higher incidences

of TB, opportunistic infection, demyelination, and lymphoma were observed with the 100 mg dose regimen across all indications; these are known risks with anti-TNF agents. The current SmPC describes the greater incidence with the 100 mg dose regimen compared with the 50 mg dose regimen.

- An analysis of the discontinuation of study agent due to an AE through Week 52, in which discontinuation of study agent due to an AE were included in the subjects' original randomized groups, showed a higher proportion of subjects discontinuing study agent in the placebo group than in either the 100 mg group or the 50 mg group.
- No new safety signals were observed with the 100 mg maintenance dose regimen in the UC population.

Laboratory findings

Haematology

Markedly abnormal post-baseline values with regard to decrease in lymphocytes were reported for 12% of golimumab and 18% of placebo treated patients in study C0524T17. Similar findings were identified in 36%, 25% and 22% of patients in the placebo, 50 mg and 100 mg treatment groups of study C0524T18.

In study C0524T18 there were 3 patients with transient decreases of neutrophils $<1.0 \times 10^3$ cells /µL.

Chemistry

Elevated potassium values were reported from 8 patients being actively treated.

ALT and AST values ≥3 x ULN were uncommon both for placebo (n=3) and golimumab treated (n=2) patients in study C0524T17. In study C0524T18 there were 3 patients with concurrent elevations in ALT and total bilirubin (>2 x ULN).

Safety in special populations

The safety of golimumab was evaluated regarding the rates of AEs, SAEs, AEs leading to discontinuation of study agent and infections in the Phase 3 UC studies in subpopulations based on demographics (i.e., sex, race, age, and weight) and baseline disease characteristics (i.e. disease severity, disease duration, and extent of disease). In general there were no differences between the subgroups. However, for age, although the number of patients ≥65 was limited, n=51 (4%) in comparison with patients <65 (n=1182, 96%), the rate of AEs, SAEs, or serious infection were higher in the older population. In patients ≥65 the rates were 86%, 29% and 6% and in the younger 78%, 15% and 4%, respectively.

Immunological events

In study C0524T17 there were 3 patients that had positive tests for antibodies to golimumab.

Among treated patients that were negative for antinuclear antibodies (ANA) at baseline, 11 were positive for ANA antibodies (using a titre ≥1:160) at week 6 (4 patients that had received golimumab and 7 placebo).

There were no patients that were positive for anti-dsDNA antibodies between baseline and at their last evaluation through week 6.

In study C0524T18, a total of 20 (4.4%) of 455 randomized patients with appropriate samples for antibodies to golimumab were positive at week 54, 11 of 155 (7.1%) subjects in the placebo group

(these subjects had received golimumab induction treatment), 4 of 152 (2.6%) subjects in the golimumab 50 mg group, and 5 of 148 (3.4%) subjects in the golimumab 100 mg group. Among the subjects who were positive for antibodies to golimumab, the majority (16/20) had titers under 1:640.

The corresponding figures for all treated patients (randomized and non-randomized patients were, of 1103 appropriate samples, 32 (2.9%) were positive, 21 of 32 had titers under 1:640.

There were 6 (2.7%) patients in the placebo group, 6 (4.3%) and 31 (3.8%) in the golimumab 50 mg and golimumab 100 mg groups, that were positive for ANA antibodies between baseline and week 54.

Discontinuation due to adverse events

In study C0524T17, 4 patients in the placebo and 3 in the active groups discontinued due to AES during the induction period. Five (5) of these patients discontinued due to an SAE (viral infection, erythema nodosum and rash, colitis ulcerative (n=2), carcinoma in situ and colon cancer (identified in biopsies prior to randomization)).

Of randomized patients in the placebo, 50 mg and 100 mg golimumab groups in study C0524T18, 6%, 5% and 9%, discontinued due to AEs. The discontinuation was due to UC flares in 2%, 4% and 4% of patients in these groups, respectively. Corresponding figures taking into account time of follow-up were 10.4, 6.2 and 10.4 per hundred patient-years.

2.5.2. Discussion on clinical safety

The most commonly reported events were flares of UC followed by nasopharyngitis and headache. Worsening of UC was the most common adverse event and was also the dominating reason for discontinuations.

There were no major differences between the two active treatment groups in numbers of AEs. However, the rate of SAEs and discontinuations due to AEs was higher in the 100 mg group than in the 50 mg group. Among patients receiving the 50 mg dose there were 8.4% that had SAEs and 5% discontinued due to AEs. Corresponding figures for patients on 100 mg were 14.3% and 9%.

The proposed treatment for UC involved higher dosing regimen than for the already approved indications. However, there are safety data from other disease populations including about one thousand patients being exposed to golimumab (100 mg) for at least one year and 760 for at least 96 weeks. Thus, although long-term safety data is sparse in the UC indication, there are safety data available for the higher dose from clinical trials in other patient populations. Furthermore, it has been concluded that the higher maintenance dose should be restricted to patients >80 kg.

Important potential risks for the UC population are colon dysplasia/colon cancer and hepatosplenic T-cell lymphoma (HSTCL). The MAH agreed to add wording on the potential risk for HSTCL and colon carcinoma/dysplasia in Section 4.4 Special Warnings and Precautions for Use of the SmPC. HSTCL has also been added as a class-effect adverse drug reaction in Section 4.8. Colon carcinoma/dysplasia and HSTCL have been added as important potential risks for golimumab in the RMP.

Safety data from patients above the age of 65 have been presented. Overall it seems elderly patients have a similar incidence of AEs and SAEs as younger patients.

2.5.3. Conclusions on clinical safety

The safety profile of golimumab is well established and is characterised by several potentially serious risks. No new safety issues were revealed in the UC clinical trials. There seems to be a dose related increase in SAEs.

Adequate risk minimisation as well as pharmacovigilance activities are in place from previous procedures. Safety data from studies in the UC programme indicated that the safety profile in the treatment of ulcerative disease is similar to that for other approved indications. There were no new safety concerns identified.

The treatment of UC is a new indication for golimumab, and long-term benefits and risks of golimumab treatment in UC are currently unknown. Potential risks of treatment of UC with biologic agents, including anti-TNFα agents, as well as conventional therapy, include colorectal dysplasia, colorectal cancers, and HSTCL. The rate at which subjects with UC have colectomies is also an important factor.

The CHMP requested the MAH to collect disease-based UC registry data as an additional pharmacovigilance activity to assess the long-term safety of golimumab in adult subjects with UC. The Nordic National Register Database Study is proposed as a registry for these purposes. A feasibility assessment will be conducted to determine whether the data from the Spanish Registry would also be useful in this regard. These measures are described in the updated RMP.

The CHMP considers the following measures necessary to address issues related to safety:

- The MAH should submit the protocol for the Ulcerative Colitis Registry within the Nordic National Registry Database for review by December 2013.

- The MAH should provide the timelines of the feasibility assessment for utilising the Registry in Spain as an additional source of information for collection of long term safety data in patients with ulcerative colitis by October 2013.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 8.5 the PRAC considers by consensus that the risk management system for golimumab (Simponi) in the treatment of:
moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA) or who are intolerant to or have medical contraindications for such therapies is acceptable provided that the MAH submits the protocol for the Ulcerative Colitis Registry within the Nordic National Registries Database for review within 6 months of the CHMP Opinion.

The MAH is also requested to provide the timelines of the feasibility assessment for utilising the Registry in Spain as an additional source of information for collection of long term safety data in patients with ulcerative colitis.

An updated RMP should be submitted before the CHMP Opinion with the available milestones for these studies.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 15: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Hypertension • Lymphoma (excluding HSTCL) • Hepatitis B virus reactivation • Congestive heart failure • Autoimmune processes • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Vasculitis • Psoriasis (new onset or worsening of pre-existing) • Melanoma
Important potential risks	• Malignancy (excluding lymphoma and melanoma) • Serious hepatotoxicity • Exposure during pregnancy • Serum sickness • Maladministration/administration error • Serious depression including suicidality • Sarcoidosis/sarcoid-like reaction • Colon carcinoma/dysplasia (in UC) • HSTCL
Missing information	• Use in paediatric patients • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a past history of latent or active TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients after recent vaccination with live

	bacterial or viral vaccine • Use in patients with active infections including HIV, hepatitis B, hepatitis C • Use in patients with recent prior use of other biologics excluding anti-TNFα agents • Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF • Use in patients with history of demyelinating disease • Use in patients with a history of lupus or lupus-like syndrome • Long-term safety data

The PRAC agreed.

Pharmacovigilance plans

Table 16: Ongoing and planned studies in the PhV development plan

Activity / Study title	Safety concerns addressed	Status	Date for submission of final reports
Long-term (5-yr) Extensions of SC Phase 3 RA, PsA, and AS Trials			
C0524T05 (RA)	Long-term safety data	Ongoing	4Q2013
C0524T06 (RA)	Long-term safety data	Ongoing	4Q2013
C0524T11 (RA)	Long-term safety data	Ongoing	4Q2013
C0524T08 (PsA)	Long-term safety data	Ongoing	4Q2013
C0524T09 (AS)	Long-term safety data	Ongoing	4Q2013
Long-term (5-yr) Extensions of SC Phase 3 RA, PsA, and AS Trials			
C0524T18 (UC)	Long-term safety data	Ongoing	TBD
Phase 3 Trial in JIA			
CNTO148JIA3001 (JIA, SC)	Use in paediatric patients	Ongoing	2015
Registry and Epidemiology Studies			
RABBIT (P04480)	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Lymphoma (excluding HSTCL)	Ongoing	TBD

	• Congestive heart failure • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Melanoma • Malignancy (excluding lymphoma and melanoma) • Serum sickness		
Swedish Database Initiative (CNTO148ART4003)	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Hypertension • Lymphoma (excluding HSTCL) • Hepatitis B virus reactivation • Congestive heart failure • Autoimmune process • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Vasculitis • Psoriasis (new onset or worsening of pre-existing) • Melanoma • Malignancy (excluding lymphoma and melanoma) • Serious hepatotoxicity • Serious depression including suicidality	Ongoing	2Q 2015

	• Sarcoidosis/sarcoid-like reaction • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a past history of latent or active TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections including HIV, hepatitis B, hepatitis C • Use in patients with recent prior use of other biologics excluding anti-TNFα agents • Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF • Use in patients with a history of demyelinating disease • Use in patients with a history of lupus or lupus-like syndrome		
OptumInsight Drug Safety Epidemiology Study (CNTO148ART4002)	• Serious infections including opportunistic infections and TB • Demyelinating disorders • Hypertension • Lymphoma (excluding HSTCL) • Hepatitis B virus	Ongoing	4Q 2017

	reactivation • Congestive heart failure • Autoimmune process • Haematologic reactions • Serious systemic hypersensitivity (including anaphylactic reaction) • Malignancy (excluding lymphoma and melanoma) • Serious hepatotoxicity • Exposure during pregnancy • Serum sickness • Serious depression including suicidality • Use in patients with hepatic impairment • Use in patients with renal impairment • Use in patients with a past history of latent or active TB • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with active infections including HIV, hepatitis B, hepatitis C • Use in patients with recent prior use of other biologics excluding anti-TNFα agents • Use in patients with concomitant diagnosis of CHF including medically controlled		

	asymptomatic CHF • Use in patients with a history of demyelinating disease • Use in patients with a history of lupus or lupus-like syndrome		
Pregnancy Research Initiative (CNTO148ART4001)	• Exposure during pregnancy	Ongoing	2Q 2015
Nordic National Register Database Study	• Colon carcinoma/dysplasia (in UC) • HSTCL • Long term safety data	Proposed	TBD

AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; RA = rheumatoid arthritis N/A = not applicable; SC = subcutaneous; TBD = to be determined

The PRAC noted the proposal outlines by the MAH for the two different registry options in UC (the Nordic National Register Database Study and the Registry in Spain.

The PRAC considered that both of these databases would be able to generate the required data including comparisons of Simponi with biologic, as well as non-biologic treatments, and possible switches between different treatments.

The PRAC recommended that the proposal for the protocol for the Nordic registry should be submitted within 6 months of the CHMP opinion.

The PRAC also requested that the time lines for the feasibility assessment for using the Spanish registry should also be outlined in a revised RMP which should be submitted .

Risk minimisation measures

Table 17: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Serious infections including opportunistic infections and TB	Guidance is provided in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC	Patient Alert Card Golimumab Educational Programme
Demyelinating disorders	Included in the Special Warnings and Precautions for Use and Undesirable Effects sections of the	None

	SmPC	
Hypertension	Included in the Undesirable Effects section of the SmPC	None
Lymphoma	Included in the Special Warnings and Precautions for Use and Undesirable Effects sections of the SmPC	None
Hepatitis B virus reactivation	Included in the Special Warnings and Precautions for Use and Undesirable Effects sections of the SmPC.	Patient Alert Card Golimumab Educational Programme
Congestive heart failure	Described in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC	Patient Alert Card Golimumab Educational Programme
Autoimmune process	Described in the Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC	None
Haematologic reactions	Described in the Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC	None
Serious systemic hypersensitivity (including anaphylactic reaction)	Described in the Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC	Golimumab Educational Programme
Vasculitis	Described in Undesirable Effects section of the SmPC	None
Psoriasis (new onset or worsening of pre-existing)	Described in Undesirable Effects section of the SmPC	None
Melanoma	Described in the Special Warnings and Precautions for Use, and Undesirable Effects sections of the SmPC	Golimumab Educational Programme
Important potential risks		
Malignancy (excluding lymphoma and melanoma)	Specific malignancies are included in the Undesirable Effects section of the SmPC. Guidance on the overall risk of malignancy and on paediatric malignancy is provided in the Special Warnings and Precautions	None

	for Use section of the SmPC.	
Serious hepatotoxicity	Included in the in Undesirable Effects section of the SmPC. Serious hepatotoxicity will continue to be monitored.	None
Exposure during pregnancy	Guidance is provided in the Fertility, Pregnancy and Lactation section of the SPC	None
Serum sickness	N/A	Golimumab Educational Programme
Maladministration /administration error	Instructions for administration are provided in the Posology and Method of Administration section and Special Precautions for Disposal and Other Handling of the SmPC and detailed instructions for patients on administration techniques are provided in the Package Leaflet.	Golimumab Educational Programme
Serious depression including suicidality	Depression is included in the Undesirable Effects section of the SmPC. Serious depression including suicidality will continue to be monitored.	None
Sarcoidosis/sarcoid-like reaction	Mentioned in Undesirable Effects section of the SmPC	None
Colon carcinoma/dysplasia (in UC)	Guidance on the overall risk of malignancy is provided in the Special Warnings and Precautions for Use section of the SmPC.	None
HSTCL	HSTCL is listed as a class effect and is mentioned in the Special Warnings and Precautions for Use and Undesirable Effects sections of the SmPC.	None
Missing information		
Use in paediatric patients	Use in paediatrics is addressed in the Posology and Method of Administration section of the SmPC. Paediatric malignancy is described in the Special Warnings and Precautions for Use section of the SmPC.	None
• Use in patients with	Guidance is provided in the Special	None

hepatic impairment • Use in patients with renal impairment • Use in patients with concurrent malignancy or a history of malignancy • Use in patients with history of demyelinating disease • Use in patients with a history of lupus or lupus-like syndrome	Warnings and Precautions for Use section of the SmPC.	
• Use in patients with a past history of latent or active TB • Use in patients with active infections including HIV, hepatitis B, hepatitis C • Use in patients with concomitant diagnosis of CHF including medically controlled asymptomatic CHF	Guidance is provided in the Contraindications and Special Warnings and Precautions for Use sections of the SmPC.	None
Use in patients after recent vaccination with live bacterial or viral vaccine	Guidance is provided in the Special Warnings and Precautions for Use, Interaction with Other Medicinal Products and Other Forms of Interaction, and Fertility, Pregnancy, and Lactation sections of the SmPC.	None
Use in patients with recent prior use of other biologics excluding anti-TNFα agents	Guidance is provided in the Special Warnings and Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction sections of the SmPC.	None
Long term safety data	N/A	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

The MAH has therefore submitted and updated RMP including the following Pharmacovigilance activities to investigate further some of the safety concerns:

Description	Due date
Submission of Nordic National Register Database Study - Protocol submission to PRAC	31 December 2013
Perform feasibility assessment of Spanish Registry (collection of data from clinical practice regarding treatment interruption will be performed)	31 October 2013

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Variation EMEA/H/C/992/WS0312/0041 submitted to add Melanoma and Merkel cell carcinoma in the Simponi EU SmPC was approved on 22 November 2012. The MAH committed as part of this variation to add melanoma as an identified risk and MCC as potential risk to the RMP of Simponi with the next RMP update. This update was made a part of the RMP approved with the II/39 variation. Following this update of the RMP, the MAH has taken the opportunity to update the information regarding the educational material in Annex II. This is agreed by the CHMP.

Furthermore, minor editorial changes have been introduced to the labelling.

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Golimumab has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (AS) since 1st October 2009.

The efficacy of golimumab for induction and maintenance treatment has been evaluated in patients with moderate to severely active ulcerative colitis. The patients had active disease despite adequate treatment with 6-MP, AZA, corticosteroids, and/or 5-aminosalicylate (5-ASA) compounds, or were intolerant to or had medical contraindications for conventional therapy.

The effect of golimumab for induction of response was evaluated after 6 weeks. Two induction studies with similar design but with different modes of administration (SC and IV) were initiated. The study using a single IV dose was prematurely stopped due to a more favourable effect of the SC induction therapy. The SC administration included two doses of the study drug at weeks 0 and 2 (200 mg/100 mg or 400 mg/200mg). For the primary efficacy endpoint clinical response, (decrease of Mayo score ≥30% and ≥3 points with decreased rectal bleeding subscore ≥1 or subscore of 0 or 1), the observed difference between golimumab and placebo was 21% and 25% for the 200 mg/100 mg and 400 mg/200 mg doses, respectively. Corresponding figures for the highest ranked secondary endpoint, induction of clinical remission (Mayo score ≤2 with no subscore >1), were 11% and 12%.

Patients in clinical response from the induction studies were invited to continue into the maintenance study. The maintenance study was of double-blind placebo-controlled design and the effect of

golimumab therapy, 50 mg and 100 mg every 4 weeks, for 52 weeks was evaluated. The observed difference between active and placebo treatment for maintaining clinical response was 16% for the 50 mg dose and 19% for the 100 mg. The difference between active and placebo treatment for patients in remission both at week 30 and 54 was 8% and 12% for the low and high dose, respectively.

The results of the induction and maintenance studies for treatment of patients with moderate to severe UC with golimumab showed a statistically significant effect on the primary efficacy endpoint that was supported with the result of major secondary endpoints. The observed differences between active and placebo treatment are considered to be clinically relevant for patients with inadequate response or intolerance to conventional therapy. Furthermore, the magnitude of effect of golimumab for induction and maintenance treatment in the UC population is similar to that of other TNF-α inhibitors.

Data has been presented showing that there were 19% and 17% of patients that were refractory to 5-ASA only in the induction and maintenance study, respectively. The rational for the inclusion of this population, that is generally not considered for anti TNF-α therapy, was to explore the effect of early intervention. Excluding these patients from the efficacy analyses did not have any major impact on the results.

Uncertainty in the knowledge about the beneficial effects

The MAH has discussed the need for recommendations as regards discontinuation of therapy in patients who have responded to treatment. The MAH stated that patients in clinical response to anti-TNF therapy are expected to have ongoing benefit from continued treatment. It is accepted that there are at present no data available to support a recommendation and the decision to continue therapy is left at the discretion of the treating specialist. Nevertheless, collection of data from clinical practice regarding treatment interruption is important and the MAH will collect additional data regarding this point the ongoing long-term extension of the C0524T18 trial and the proposed Nordic National Register Database Study and the Spanish Registry (as detailed in the RMP).

Risks

Unfavourable effects

The safety profile of golimumab is well established and is characterised by several potentially serious risks, including infections and potential risks of lymphoproliferative disorders and malignancies, congestive heart failure and demyelinating disorders. Adequate risk minimisation as well as pharmacovigilance activities are in place from previous procedures.

Safety data from studies in the UC programme indicated that the safety profile in the treatment of ulcerative disease seems to be similar to that for other approved indications. There were no new safety concerns identified. The most commonly reported events were flares of UC followed by nasopharyngitis and headache. Worsening of UC was the most common adverse event and was also the dominating reason for discontinuation. The SmPC contains recommendations to stop treatment in subjects who do not respond within a defined time frame.

Uncertainty in the knowledge about the unfavourable effects

Long-term safety data from the UC indication is sparse, in particular for the proposed maintenance dose 100 mg, which also is higher than what has previously been approved for other indications. Data from other disease populations have been presented, which include safety data from one thousand

patients being exposed to golimumab (100 mg) for at least one year and 760 for at least 96 weeks. The presented safety experience from other indications gives a sign of numerically higher rates of events of special interest with the 100 mg dose than with the 50 mg dose.

Although overall no new safety signals have been identified in the presented studies, follow-up on the limited long-term safety is of importance. In response to a question regarding a registry, the MAH has submitted outlines for two registry options addressing the use of golimumab in the treatment of active moderate to severe UC in adult patients(as detailed in the RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The observed differences in efficacy between placebo and active treatment show that there is an effect of golimumab in patients with moderate to severe ulcerative colitis. The demonstrated effect is considered to be of clinical relevance for patients that have previously failed conventional therapies.

Treatment with golimumab and also alternatives for ulcerative colitis is associated with potentially serious adverse events. Main concerns regarding treatment with golimumab are the increased risk of infections and potential risks of lymphoproliferative disorders and malignancies, congestive heart failure and demyelinating disorders. A special concern in young adults with ulcerative colitis for treatment with TNF-α inhibitors, is the potential risk of developing hepatosplenic T-cell lymphoma (HSTCL). These risks have been addressed in the updated RMP and the PI.

Benefit-risk balance

The benefit-risk balance of golimumab use in ulcerative colitis is positive.

Discussion on the Benefit-Risk Balance

The results show statistically significant effects of golimumab in inducing and maintaining response/remission in patients with moderate to severe ulcerative colitis. The observed differences between active and placebo treatment are considered to be of clinical relevance for patients who have experienced inadequate response to conventional therapies.

Considering the potentially serious safety profile of golimumab it has been agreed that the higher maintenance dose should be restricted to patients >80 kg. Data has been presented supporting a gain in efficacy with the 100 mg dose for those patients compared with the 50 mg q4w dose

The MAH has updated the Product Information and has accepted the CHMP comments. An updated RMP has been submitted in accordance with the PRAC's recommendations.

4. Recommendations

Final 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:

Variation(s) accepted		Type
C.1.6 a	Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include new indication/population for Simponi for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

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 accordingly.

Editorial changes have been made to the labelling.

Following the update of the RMP, the MAH has taken the opportunity to update the information regarding the educational material in Annex II.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product.

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP. An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Simponi are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Simponi,

- The need to evaluate patients for both active and inactive tuberculosis prior to starting the treatment, including use of appropriate screening tests,
- The contraindication of Simponi in patients with history of moderate to severe heart failure (NYHA III/IV), and potential risk of congestive heart failure being worsened by Simponi,
- The risk of acute injection-related reactions and delayed serious systemic hypersensitivity reactions, the need for instructing patients on techniques for administration, and guidance for Health Care Professionals on how to report administration errors,
- The recommendation for periodic skin examinations, particularly for patients with risk factors for skin cancer.
- The role and use of patient alert card.

5. EPAR changes

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

Scope

Extension of Indication to include new indication/population for Simponi for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

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 accordingly.

Editorial changes have been made to the labelling.

Following the update of the RMP, the MAH has taken the opportunity to update the information regarding the educational material in Annex II.

Summary

Please refer to Scientific Discussion Simponi/H/C/992/II/39 for further information.