14 April 2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Simponi

golimumab

Procedure No.: EMEA/H/C/000992/II/0021

Note

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

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Scientific discussion

Introduction

Golimumab is approved in the EU in adults who have responded inadequately to previous therapy for the treatment of moderate to severe active rheumatoid arthritis (RA) in combination with methotrexate (MTX); active and progressive psoriatic arthritis (PsA), alone or in combination with MTX; and severe, active ankylosing spondylitis (AS).

For PsA and AS, the approved dose is 50 mg given once a month. The currently approved dose in RA is: 50 mg given once a month, on the same date each month. Simponi should be given concomitantly with MTX.

Across all indications, in patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

The MAH submitted a variation to add the following indication in section 4.1 (underlined text is the wording applied for in this variation):

"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 also been shown to <u>reduce the rate of progression of peripheral joint damage as measured by X-ray and to</u> improve physical function ~~in this patient population~~."

Furthermore, the MAH also proposes an update of section 5.1 regarding golimumab's continued efficacy in the maintenance of the improvement in signs and symptoms and physical function in PsA patients. The Package Leaflet is updated accordingly.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No. 1901/2006 as amended, the application included an EMA decision (P/84/2010) for the following conditions:

- Juvenile idiopathic arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Rheumatoid arthritis

On the agreement of a paediatric investigation plan (PIP) with a deferral.

The PIP is not yet completed.

Clinical aspects

Clinical pharmacology

Golimumab is a human monoclonal antibody with an immunoglobulin G (IgG) 1 heavy chain isotype (G1m allotype) and a kappa light chain isotype. Golimumab binds with high affinity to both soluble and transmembrane forms of tumor necrosis factor alpha and inhibits TNF bioactivity.

Clinical efficacy

Introduction

The initial marketing authorization application and approval were based primarily on 24-week safety and efficacy data from one Phase 3 PsA study with SC golimumab, C0524T08. During the approval procedure, 52 weeks efficacy data were submitted as part of responses to Day 120 LoQ. Thus, focus of the efficacy assessment will be data beyond week 52 as well as the X-ray data.

Study C0524T08 (GO-REVEAL)

Methods

For details on this study, see the original approval assessment reports. In brief:

- Study Participants: Men and women, >18 years of age, with a diagnosis of PsA for at least 6 months prior to first study agent administration who had active PsA despite current or previous DMARD or NSAID therapy, and who had not previously been treated with anti-tumor necrosis factor (TNF) α therapy.

- The main inclusion criteria were: Active PsA at the time of screening and at baseline, as characterized by 3 or more swollen joints and 3 or more tender joints, and despite current or previous DMARD or NSAID therapy. DMARD therapy was defined as taking a DMARD for at least 3 months, or evidence of DMARD intolerance. NSAID therapy was defined as taking an NSAID for at least 4 weeks. Presence of at least 1 of the PsA subsets: DIP joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.

- Study population: The median age was 47 years and 60% of enrolled subjects were men. Subjects had long-standing disease (about 5 years of median duration) of moderate to severe activity. Polyarthritis symmetric was the more frequent subtype of PsA, more than one third of the study population was affected by dactylitis and/or enthesitis at baseline and the majority had psoriatic fingernail disease. The proportions of subjects at baseline using MTX, oral corticosteroids, or NSAIDs specifically for PsA were similar across all treatment groups. Approximately half of the subjects in each treatment group were receiving MTX at baseline with a median dose of 15 mg/week. About 3/4 were taking NSAIDs, and less than 20% oral corticosteroids. Patients were stratified by MTX use at baseline. The treatment groups were well balanced with respect to baseline demographics and disease characteristics.

Treatment:

The first 24 weeks were placebo-controlled; the following treatments were given:

- Group I: Placebo SC injections at Weeks 0, 4, 8, 12, 16, and 20
- Group II: Golimumab 50 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20
- Group III: Golimumab 100 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20

Early Escape (Week 16)
At Week 16, subjects in any group who had < 10% improvement from baseline in both swollen and tender joint count entered early escape in a double-blinded fashion, with the following treatments:

- Group I: Golimumab 50 mg SC injections at Weeks 16 and 20
- Group II: Golimumab 100 mg SC injections at Weeks 16 and 20

Subjects randomized to Group III, and qualifying for early escape, continued to receive golimumab 100 mg SC injections at Weeks 16 and 20.

At Week 24: the following treatments were given

- Group I: Golimumab 50 mg SC injections at Week 24 and every 4 weeks thereafter through Week 48; if entered into early escape, subjects continued to receive golimumab 50 mg injections every 4 weeks through Week 48.

- Group II: Continued golimumab 50 mg SC injections at Week 24 and every 4 weeks thereafter through Week 48; if entered into early escape, subjects continued to receive golimumab 100 mg injections every 4 weeks through Week 48.

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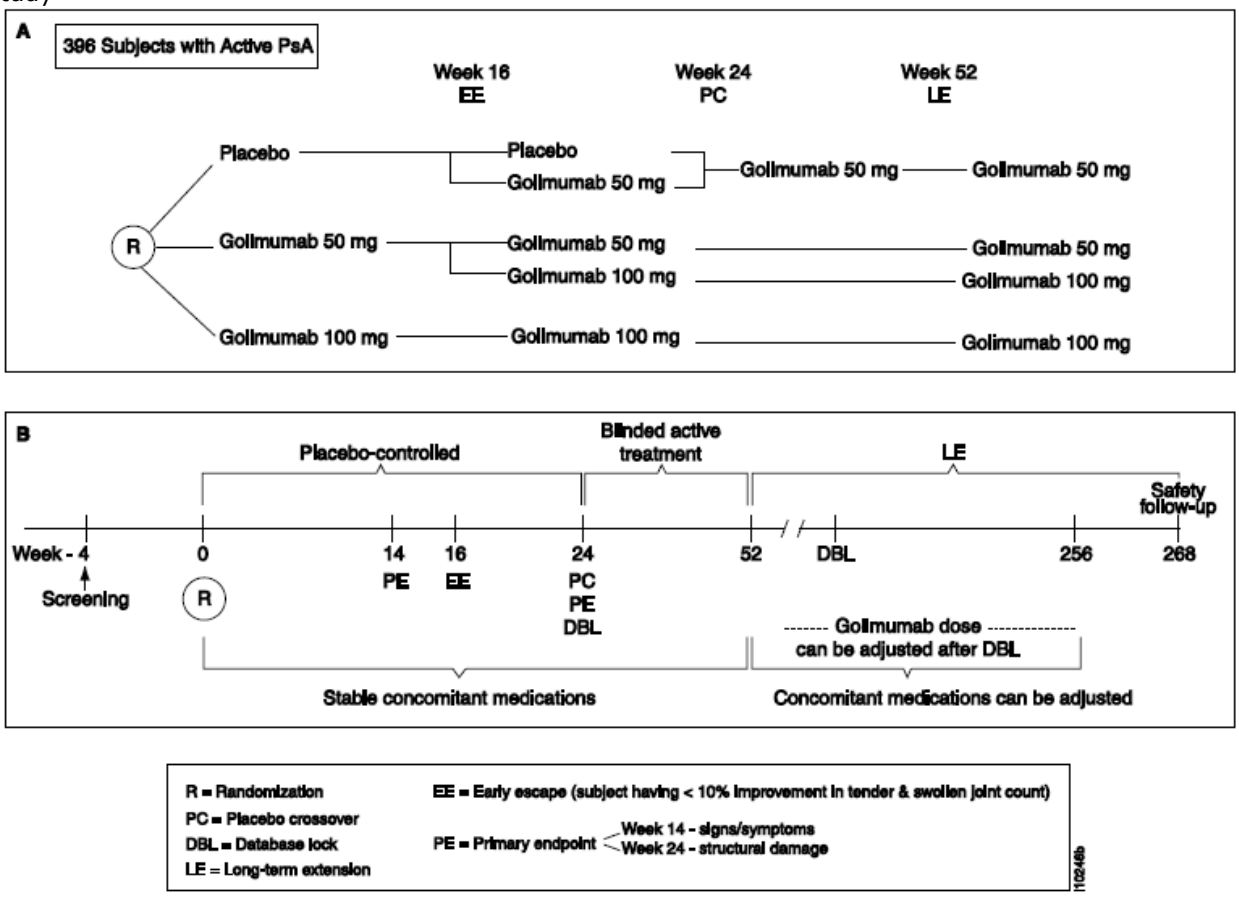
- Group III: Continued golimumab 100 mg SC injections at Week 24 and every 4 weeks thereafter through Week 48; if entered into early escape, subjects continued to receive golimumab 100 mg injections every 4 weeks through Week 48.

Figure 1 Study scheme. Panel A shows study treatments; Panel B shows key time points during the study



From week 52, patients entered a *Long-term extension period* (Weeks 52 through 268), given open-label treatment after the Week 52.

Two co-primary endpoints were used:

- The number of subjects who achieved an ACR 20 (American College of Rheumatology 20) response at Week 14.
- change from baseline in total PSA modified vdH-S score (referred to as total modified van der Heijde-Sharpe score) for hands and feet at Week 24

A number of additional endpoints were evaluated addressing signs and symptoms of arthritis, psoriasis, physical function, quality of life, and structural damage, see previous AR.

Assessment of structural damage

The 2 primary readers, and an adjudicator when required per the imaging charter, independently read each subject's radiographs in a blinded fashion. All images for a given subject (ie, baseline, Week 24, Week 52, and any radiographic taken at the time of SC study agent discontinuation) were read as a group in a random order; the readers were blinded to randomized treatment group, the subject's demographics and the time point at which individual radiographs were obtained.

The PsA modified vdH-S scoring method evaluated hand and feet erosions and joint space narrowing (JSN) with a total score ranging from 0 to 528. This method is based on the original vdH-S scoring method used in RA trials (van Der Heijde et al, 1992), with the addition of distal interphalangeal joints in the hands, and evaluation for PsA specific radiographic features such as pencil-in-cup (PIC) and gross osteolysis (GO) (van der Heijde et al, 2005). It was previously used in other PsA trials with anti-TNFα agents and is accepted by regulatory agencies and the rheumatology community as a method to assess the progression of structural damage in PsA (van der Heijde et al, 2007 and Antoni et al, 2008).

Statistical methods

Descriptive statistics, such as the mean, median, SD, range, and the interquartile range (IQ range) for continuous variables, and counts and percentages for categorical variables were used to summarize most data.

All statistical testing was 2-tailed, at a significance level of 0.05. In addition to statistical analyses and tabulated descriptive statistics, graphical data displays, and subject listings were also used to summarize/present the data. Complete data handling rules for each endpoint are described in the SAP. SAS (Version 8.2) was used to conduct these analyses.

The co-primary efficacy and selected secondary efficacy analyses were based on all subjects who were randomized at Week 0; i.e., the intent-to-treat population. Based on the intent-to-treat principle, subjects randomly assigned to a treatment group were included in the efficacy analyses according to their assigned treatment group whether or not they received the assigned treatment.

Co-primary Radiographic Analysis

For the co-primary analysis, data were summarized by randomized treatment groups:

- Placebo: Subjects randomized to the placebo group
- Golimumab 50 mg: Subjects randomized to the golimumab 50 mg group
- Golimumab 100 mg: Subjects randomized to the golimumab 100 mg group

For selected radiographic efficacy parameters, data were summarized by randomized treatment groups. Other radiographic data were summarized by early escape or crossover status within randomized treatment groups. Analyses were based on data with no missing imputation rules applied unless specified otherwise.

Data Handling Rules

Treatment failure rule will not be applied.

Slotting for images taken outside of visit windows

All radiographs have to be taken within a protocol-specified window of ± 4 weeks of the baseline and ± 2 weeks for subsequent visits at Week 24, Week 52, Week 104, Week 184 and Week 256 visits. Nominal visits will still be used if the images taken within ± 8 weeks of the scheduled visit date. The images that are taken outside ± 8 weeks of the scheduled visit date will be considered out-of-window, and the x-ray data will be set to missing for that scheduled visit.

Early escape rule:

For subjects who meet early escape criteria at Week 16 in Groups I and II, their Week 24 values will still be used for Week 24 analysis, though these subjects have a change in their dose.

Missing data imputation rules

- If both baseline and Week 24 total modified vdH-S scores are missing, the change from baseline in total modified vdH-S scores at Week 24 will be imputed with the median change from baseline in total modified vdH-S scores of all subjects in the same stratum at Week 24.
- If baseline total modified vdH-S score is missing, but data are available for 2 time points during the period from Week 0 to Week 24 (including any out-of-window or SC study agent discontinuation visit), the total modified vdH-S scores at these 2 time points will be linearly extrapolated to impute the missing score at baseline. If there is not enough data for linear extrapolation, then the change from baseline in total modified vdH-S scores at Week 24 will be imputed with the median change from baseline in total modified vdH-S scores of all subjects in the same stratum at Week 24.

• If Week 24 total modified vdH-S score is missing, but data are available for 2 time points during the period from Week 0 to Week 24 (including any out-of-window or SC study agent discontinuation visit), the total modified vdH-S scores at these 2 time points will be linearly extrapolated to impute the missing score at Week 24. If there is not enough data in period from Week 0 to Week 24, but data are available for 2 time points during the period from Week 24 to Week 52 (including any out-of-window or SC study agent discontinuation visit), the total modified vdH-S scores at these 2 time points will be linearly extrapolated to impute the missing score at Week 24. If there is not enough data for linear extrapolation in either periods, then the change from baseline in total modified vdH-S scores at Week 24 will be imputed with the median change from baseline in total modified vdH-S scores of all subjects in the same stratum at Week 24.

Sensitivity analyses for structural damage

1. The first sensitivity analysis will be performed similarly to the co-primary analysis to assess the effect of considering only subjects who complete 24 Weeks of SC study agent administrations, did not miss any dose, and have no missing data either at baseline or Week 24.
2. The second sensitivity analysis will be performed in a similar manner as the co-primary analysis to assess the effect of considering only subjects who do not meet the early escape criteria at Week 16.
3. The third sensitivity analysis was performed similarly to the co-primary analysis to assess the effect of using the 2 primary readers' scores only, even in the cases where adjudication was employed.

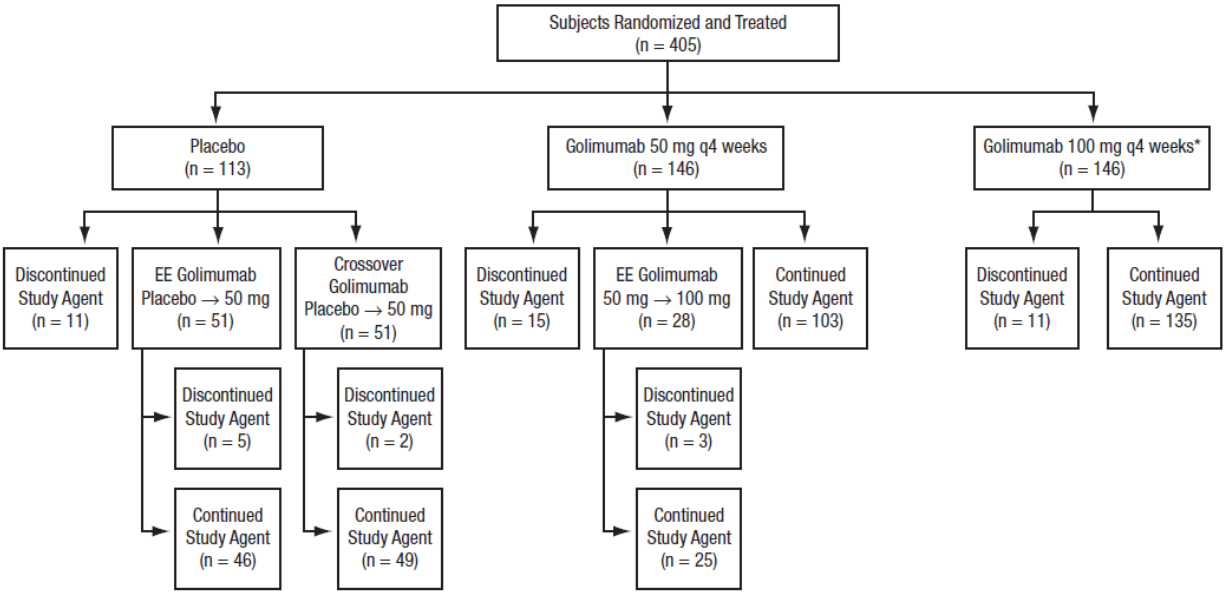
Further to the above, the CHMP noted that depending on the actually observed pattern of missing values neither the primary analysis nor the sensitivity analyses are necessarily conservative. The need for additional alternative analyses is discussed below.

Results

Disposition of patients

Figure 2 shows the study disposition throughout w 52. Up to 52 weeks 18, 18, and 11 patients discontinued study treatment in the placebo, 50 mg, and 100 mg group, respectively. Of those randomised to placebo, 50 mg, and 100 mg, an additional 7, 10, and 8 patients, respectively, discontinued study treatment between week 52 and 104. The reason for discontinuation is presented in Table 1.

Figure 2 Disposition of patients throughout week 52



EE = Early Escape
*25 subjects in this group met early escape criteria at Week 16 and continued to receive 100 mg golimumab

Table 1 Reason for discontinuation of study treatment through week 104.

		Golimumab			
	Placebo	50 mg	100 mg	Combined	Total
Subjects randomized	113	146	146	292	405
Subjects who discontinued study agent	25 (22.1%)	28 (19.2%)	17 (11.6%)	45 (15.4%)	70 (17.3%)
Reason for discontinuation					
Initiated protocol-prohibited medication	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse event	9 (8.0%)	8 (5.5%)	10 (6.8%)	18 (6.2%)	27 (6.7%)
Worsening of PsA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unsatisfactory therapeutic effect	6 (5.3%)	5 (3.4%)	4 (2.7%)	9 (3.1%)	15 (3.7%)
Lost to follow-up	1 (0.9%)	4 (2.7%)	1 (0.7%)	5 (1.7%)	6 (1.5%)
Death	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Other	9 (8.0%)	10 (6.8%)	2 (1.4%)	12 (4.1%)	21 (5.2%)

The CHMP noted the modest number of discontinuations by week (104), in total 17%. There were no major differences between placebo and the approved 50 mg group, neither with respect to the amount of discontinuations nor the cause for discontinuation.

Baseline Radiographic Characteristics
Baseline vdH-S scores were well balanced across all treatment groups with mean values ranging from 18.2 to 23.8 and median values ranging from 9.0 to 10.5 on a scale ranging from 0 to 528, indicating the presence of structural damage at baseline in this moderately to severely active PsA population.

Primary results on structural damage (week 24)

A statistically significant difference was seen between golimumab and placebo in the primary analysis of change from baseline in van der Heijde Modified Sharp score at Week 24 (Table 2).

Table 2 Summary of change from baseline in total modified van der Heijde Sharp score at Week 24 stratified by baseline MTX use; randomized subjects.

		Golimumab		
	Placebo[a]	50 mg[a]	100 mg	Combined
Subjects randomized	113	146	146	292
Change from baseline				
N	113	146	146	292
Mean ± SD	0.27 ± 1.259	-0.16 ± 1.309	-0.02 ± 1.322	-0.09 ± 1.315
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(-4.5, 6.5)	(-7.1, 5.0)	(-9.2, 4.5)	(-9.2, 5.0)
p-value		0.011	0.086	0.015

a) includes patients qualified for early escape.

Sensitivity analyses
Three sensitivity analyses were performed for the primary endpoint of change from baseline in total modified vdH-S score at Week 24. All sensitivity analyses confirmed the results of the primary analysis (See Table 3 and 4 for the first two sensitivity analyses).

Table 3 Change from baseline in van der Heijde Modified Sharpe score at week 24. Sensitivity analysis 1 including only patients who completed study treatment through Week 24, did not miss any dose, and had no missing data either at baseline or at Week 24.

		Golimumab		
	Placebo[b]	50 mg[b]	100 mg	Combined
Subjects randomized	113	146	146	292
Change from baseline				
n	93	127	130	257
Mean ± SD	0.32 ± 1.357	-0.13 ± 1.259	0.00 ± 1.286	-0.07 ± 1.272
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(-0.50, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(-4.5, 6.5)	(-5.5, 5.0)	(-9.2, 4.5)	(-9.2, 5.0)
p-value		0.012	0.112	0.017

Table 4 Change from baseline in van der Heijde Modified Sharpe score at week 24. Sensitivity analysis 2 including only patients who did not meet early escape criteria at Week 16 and therefore did not have a change in treatment regimen.

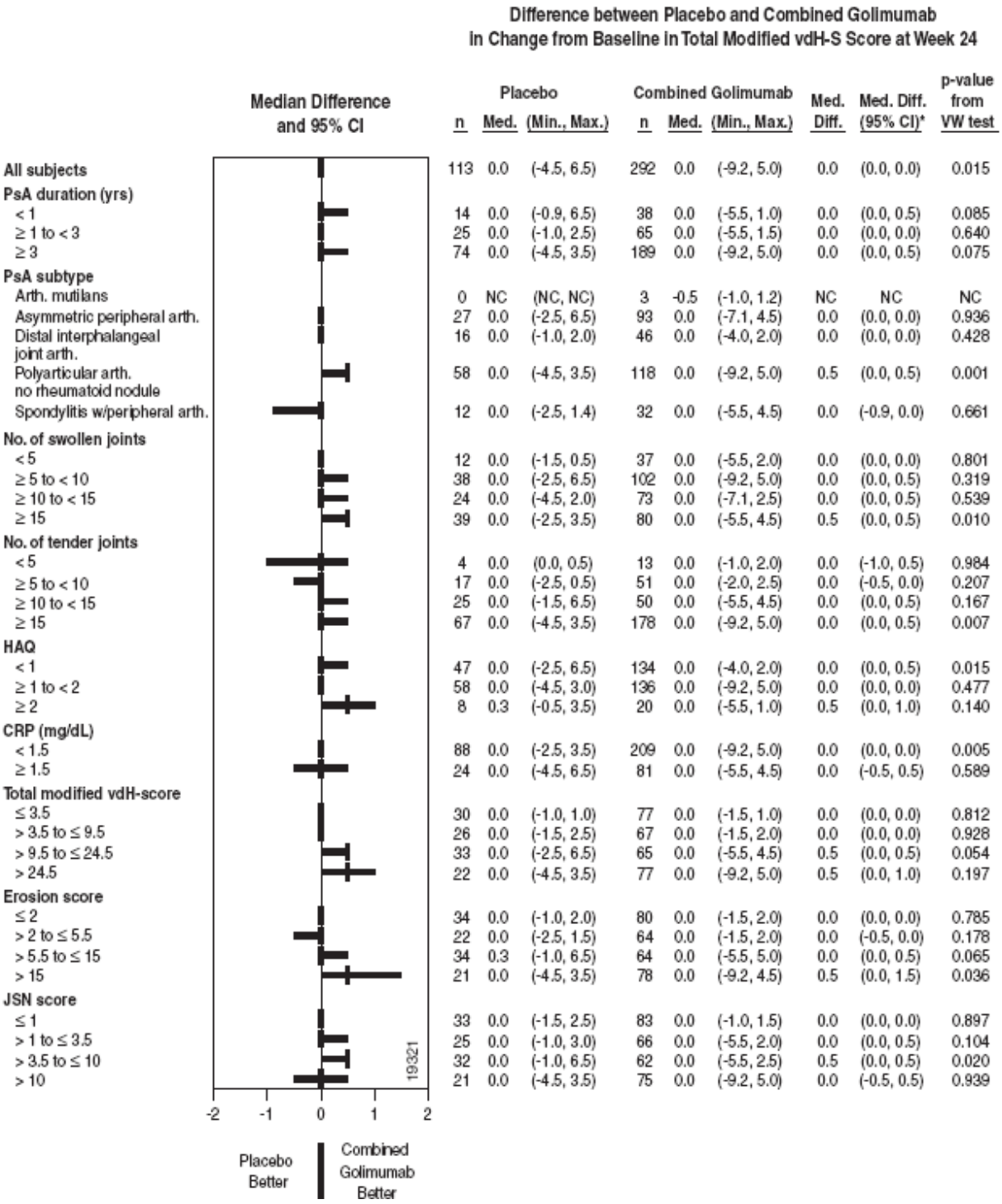
		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Change from baseline				
n	62	118	146	264
Mean ± SD	0.27 ± 1.002	-0.23 ± 1.296	-0.02 ± 1.322	-0.11 ± 1.312
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(-2.5, 3.5)	(-7.1, 2.5)	(-9.2, 4.5)	(-9.2, 4.5)
p-value		0.005	0.062	0.013

The third sensitivity analysis was performed to assess the effect of not using adjudication. In the analysis based on data from the primary readers only, results similar to the primary results was obtained.

The CHMP notes that a consistent statistically significant mean difference between golimumab 50 mg and placebo has been demonstrated in the primary analysis and the sensitivity analyses. With the similar pattern of missing values with respect to amount and cause there is no reason to believe that the observed differences are due to any substantial bias in favour of the placebo group. There was a tendency that patient discontinued earlier in the placebo group, but that should not have any disturbing impact on the imputation of missing modified vdHS scores. Thus a reliable statistically significant effect of golimumab 50 mg on structural damage has been demonstrated at week 24. However, the observed mean difference does not allow any assessment of clinical relevance.

Subgroup Analyses
At Week 24, subgroup analyses were performed for the change from baseline in total modified vdH-S score by weight, disease characteristics, geographic location, and concomitant medications for PsA. The subgroup results were consistent across golimumab treatment groups. Subgroup analyses were supportive of the primary endpoint analysis (Figure 3 and 4).

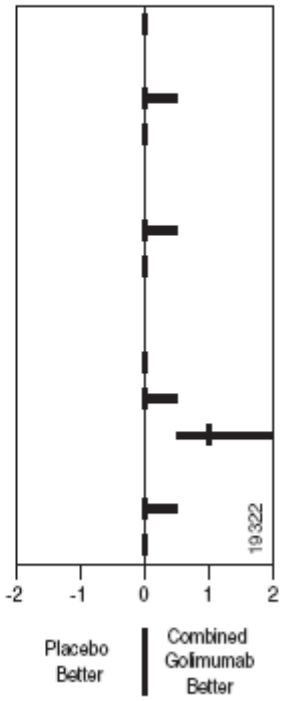
Figure 3 Median of the differences between treatment groups in change from baseline in total modified vdH-S score at Week 24 (vertical bars) in combined and placebo groups and associated 95% confidence intervals for subgroups defined by baseline characteristics; randomized subjects



The CHMP noted that only in the polyarticular arthritis subgroup, any effect on total modified Sharp score is seen; i.e. it is the only group with progression in the placebo group, which is not unexpected based on the similarity of this subgroup with the RA population. This has also been evident for other anti-TNFs.

Figure 4 Median of the differences between treatment groups in change from baseline in total modified vdH-S score at Week 24 (vertical bars) in combined golimumab and placebo group and associated 95% confidence intervals for subgroups defined by baseline medication; randomized subjects

Difference between Placebo and Combined Golimumab in Change from Baseline in Total Modified vdH-S Score at Week 24



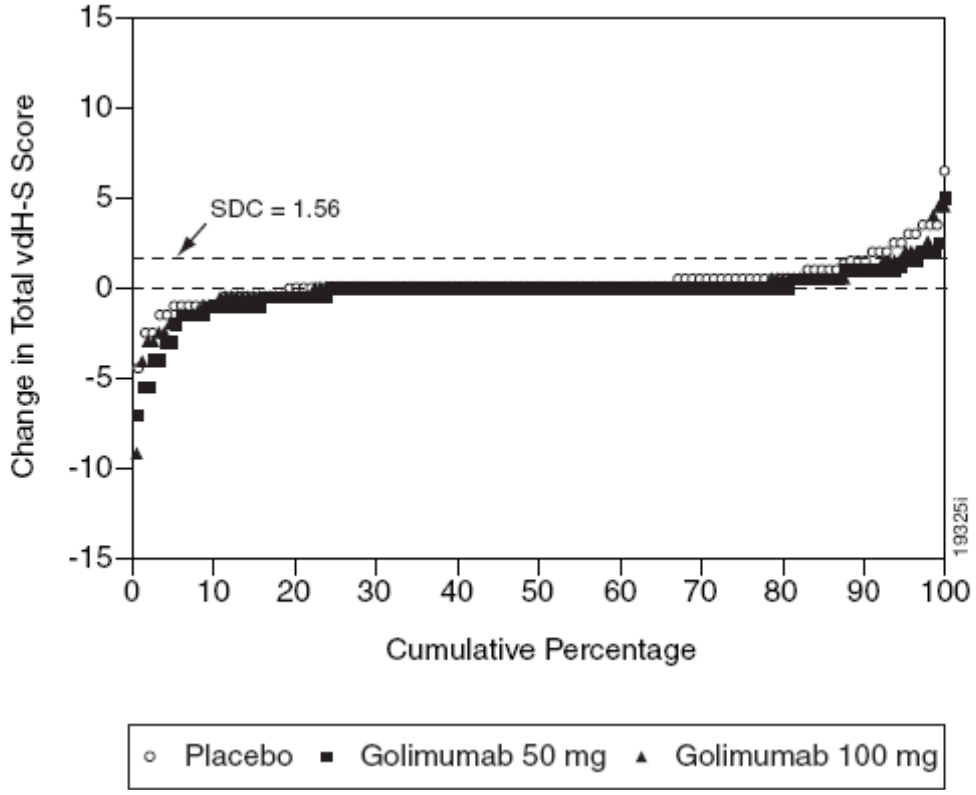
	Placebo			Combined Golimumab			Med. Diff.	Med. Diff. (95% CI)*	p-value from VW test
	n	Med.	(Min., Max.)	n	Med.	(Min., Max.)			
All subjects	113	0.0	(-4.5, 6.5)	292	0.0	(-9.2, 5.0)	0.0	(0.0, 0.0)	0.015
MTX at baseline									
Yes	54	0.0	(-4.5, 3.5)	140	0.0	(-9.2, 2.0)	0.0	(0.0, 0.5)	0.007
No	59	0.0	(-2.5, 6.5)	152	0.0	(-7.1, 5.0)	0.0	(0.0, 0.0)	0.352
Oral Corticosteroids at baseline									
Yes	19	0.0	(-1.5, 3.0)	46	0.0	(-4.1, 2.0)	0.0	(0.0, 0.5)	0.113
No	94	0.0	(-4.5, 6.5)	246	0.0	(-9.2, 5.0)	0.0	(0.0, 0.0)	0.048
Number of DMARDS used in the past									
None	28	0.0	(-1.0, 2.5)	63	0.0	(-7.1, 4.5)	0.0	(0.0, 0.0)	0.962
1 or 2	75	0.0	(-4.5, 6.5)	210	0.0	(-9.2, 5.0)	0.0	(0.0, 0.5)	0.097
3 or more	10	0.8	(0.0, 3.5)	19	0.0	(-2.5, 1.2)	1.0	(0.5, 2.0)	<0.001
NSAIDs at baseline									
Yes	88	0.0	(-2.5, 6.5)	220	0.0	(-9.2, 5.0)	0.0	(0.0, 0.5)	0.007
No	25	0.0	(-4.5, 3.0)	72	0.0	(-5.5, 2.0)	0.0	(0.0, 0.0)	0.942

*Median difference and its 95% CI are estimated with Hodges-Lehman method.

Empirical Cumulative Distribution

Figure 5 shows the empirical cumulative distribution function plot through Week 24 summarizing the change in total modified vdH-S score from baseline in individual subjects. The plot of the empirical cumulative distribution function shows that the curve of the placebo group is above that of both the golimumab 50 mg and 100 mg groups, especially in the right tail of the distribution indicating greater radiographic progression in the placebo group than in the golimumab groups.

Figure 5 Cumulative distribution plot of Modified van der Heijde Sharpe data at week 24.



The CHMP is of the opinion that although indicative of a positive effect on structural damage, 24 weeks is too short for a cumulative distribution plot to provide any useful information for discussing clinical relevance.

Structural damage data by type of damage
The change from baseline in modified vdH-S score at Week 24 by type of damage (ie, erosion and JSN) is provided in Table 5.

Table 5 Change from baseline in Modified van der Heijde Sharpe score at week 24 by type of damage.

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Change from baseline				
Both hands and feet				
Erosion score				
n	102	132	137	269
Mean ± SD	0.32 ± 0.947	-0.09 ± 0.922	-0.04 ± 0.952	-0.07 ± 0.936
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(-2.5, 3.5)	(-5.5, 2.0)	(-5.5, 3.6)	(-5.5, 3.6)
p-value		< 0.001	0.001	< 0.001
JSN score				
n	102	132	137	269
Mean ± SD	-0.03 ± 0.689	-0.03 ± 0.584	0.06 ± 0.608	0.01 ± 0.597
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(-3.0, 4.5)	(-2.0, 3.0)	(-3.7, 2.5)	(-3.7, 3.0)
p-value		0.607	0.344	0.844

Further to the above-data, the CHMP stated that the effect demonstrated on Modified vdHS Total score is entirely due to an effect on erosion score. The lack of effect on joint space narrowing is not unexpected in a study of 24 weeks duration.

Responder analysis
There were more patients with no further progression of structural damage at week 24 in the golimumab groups compared to the placebo group (Table 6).

Table 6 Percentage of patient with no further progression of structural damage at week 24.

		Golimumab		
	Placebo[a]	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Total modified vdH-S score				
n	102	132	137	269
Subjects with change in the total modified vdH-S score ≤ 0	64 (62.7%)	104 (78.8%)	105 (76.6%)	209 (77.7%)
p-value		0.007	0.020	0.003

[a] Includes subjects who qualified for early escape.

The CHMP stated that in a study with placebo-controlled phase of only 24 weeks duration the percentage of patients with no further deterioration is the only reasonable responder analysis and found it not obvious why the analysis is not based on the number of randomised patients. However counting the excluded patients as non-responders would not change the results. This analysis gives

some indication that there is a number of patients that could have a clinically relevant beneficial effect on structural damage.

Efficacy data beyond week 24
The results of the analysis of the change from baseline in total modified vdH-S scores Week 52 and 104 with missing baseline data imputation rules applied is shown in Table 7.

Table 7 Summary of change from baseline in total modified van der Heijde Sharp score at Week 52 and Week 104 (with imputation rules applied to all time points).

		Golimumab		
	Placebo[a]	50 mg[b]	100 mg	Combined
Change from baseline at Week 52[d]				
n	89	119	130	249
Mean ± SD	0.25 ± 2.621	0.28 ± 7.450	-0.37 ± 2.079	-0.06 ± 5.363
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.50)	(-0.50, 0.00)	(0.00, 0.00)	(-0.50, 0.00)
Range	(-5.0, 17.0)	(-7.0, 78.6)	(-11.0, 8.5)	(-11.0, 78.6)
Change from baseline at Week 104[d]				
n	89	120	130	250
Mean ± SD	0.22 ± 3.666	0.19 ± 7.471	-0.33 ± 2.229	-0.08 ± 5.415
Median	0.00	0.00	0.00	0.00
IQ range	(-0.50, 0.50)	(-1.00, 0.00)	(-0.50, 0.00)	(-0.50, 0.00)
Range	(-9.0, 24.0)	(-7.0, 78.0)	(-10.8, 9.0)	(-10.8, 78.0)

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

The lack of mean difference between golimumab and placebo is proposed to be explained by an imputed change from baseline of 78.6. In a sensitivity analysis without imputations the difference between 50 mg and placebo was consistent with the week 24 result.

The percentage of patients with no further progression at week 52 and 104 is presented in Table 8 and 9.

Table 8 Number of patients with no further progression of structural damage between baseline and week 52.

	Placebo → Golimumab 50 mg			Golimumab 50 mg		
	Early Escape (Week 16-52)[a]	Crossover (Week 24-52)[b]	Combined	50 mg Only[c]	Early Escape (50 mg → 100 mg)[a]	Golimumab 100 mg
Subjects randomized	51	62	113	118	28	146
Total modified vdH-S score						
n	46	48	94	101	25	134
Subjects with change in the total modified vdH-S score ≤ 0	31 (67.4%)	31 (64.6%)	62 (66.0%)	78 (77.2%)	19 (76.0%)	99 (73.9%)

[a] Subjects in these groups met the early escape criteria at Week 16.
[b] Subjects in this group crossed over at Week 24.
[c] Subjects in this group did not meet the early escape criteria at Week 16.

Table 9 Number of patients with no further progression of structural damage between baseline and week 104.

		Golimumab		
	Placebo[a]	50 mg[b]	100 mg	Combined
Randomized subjects (Reading Session 2)[c]	89	120	130	250
Total modified vdH-S score ≤ 0				
n	85	114	125	239
Subjects with change in the total modified vdH-S score ≤ 0	62 (72.9%)	88 (77.2%)	96 (76.8%)	184 (77.0%)

[a] Includes subjects who early escaped at Week 16 or crossed over at Week 24 to receive golimumab 50 mg or dose escalated after Week 52 database lock to receive golimumab 100 mg.
[b] Includes subjects who early escaped at Week 16 or dose escalated after Week 52 database lock to receive golimumab 100 mg.
[c] Includes subjects who had at least one total modified vdH-S score post Week 52.

The CHMP noted that since all patients were treated with active treatment from week 24 no increasing effect on structural damage can be expected at week 52 and 104. At best a sustained difference between patients initially randomised to active treatment and placebo could be expected. The explanation for the lack of mean difference between 50 mg and placebo (imputation of an extreme value) can be accepted by the CHMP in the light of the sensitivity analysis without imputations and the responder results (which are not sensitive to extreme values) in Table 8 and 9 showing that the 24 week responder rate at week 24 for the 50 mg dose is maintained at week 52 and 104. The observed increased responder rate in the initial placebo group must be due to a higher withdrawal rate among non-responders at week 24, since an initial no-responder cannot be expected to become a responder after switching to active treatment.

Other endpoints at week 104

In this application the MAH applies for several additions to section 5.1 based on results from the open label extension part of this study. Only results related to the proposed additions to the SPC are addressed below; namely ACR 20/50/70 response, PASI75, HAQ and DAS28.

ACR 20, ACR 50, and ACR 70 Response After Week 52 Through Week 104

The proportion of golimumab treated subjects who achieved ACR 20, ACR 50, and ACR 70 responses after Week 52 through Week 104 by treatment group is presented in Table 10.

Table 10 Number of subjects who achieved ACR 20, ACR 50, and ACR 70 responses after Week 52 through Week 104; randomized subjects who received golimumab

	Golimumab			
	Placebo → 50 mg	50 mg Only	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab[a]	95	103	25	135
Subjects in response[b]				
Week 64				
n	94	100	25	133
ACR 20	66 (70.2%)	75 (75.0%)	11 (44.0%)	97 (72.9%)
ACR 50	40 (42.6%)	62 (62.0%)	6 (24.0%)	70 (52.6%)
ACR 70	27 (28.7%)	41 (41.0%)	3 (12.0%)	39 (29.3%)
Week 76				
n	91	98	25	132
ACR 20	64 (70.3%)	73 (74.5%)	10 (40.0%)	95 (72.0%)
ACR 50	46 (50.5%)	57 (58.2%)	6 (24.0%)	66 (50.0%)
ACR 70	27 (29.7%)	36 (36.7%)	3 (12.0%)	42 (31.8%)
Week 88				
n	84	94	36	132
ACR 20	68 (81.0%)	76 (80.9%)	18 (50.0%)	100 (75.8%)
ACR 50	46 (54.8%)	59 (62.8%)	9 (25.0%)	70 (53.0%)
ACR 70	29 (34.5%)	40 (42.6%)	4 (11.1%)	46 (34.8%)
Week 100				
n	71	82	56	130
ACR 20	49 (69.0%)	66 (80.5%)	35 (62.5%)	94 (72.3%)
ACR 50	35 (49.3%)	47 (57.3%)	17 (30.4%)	64 (49.2%)
ACR 70	22 (31.0%)	35 (42.7%)	11 (19.6%)	41 (31.5%)
Week 104				
n	61	70	76	130
ACR 20	44 (72.1%)	64 (91.4%)	43 (56.6%)	95 (73.1%)
ACR 50	31 (50.8%)	46 (65.7%)	27 (35.5%)	70 (53.8%)
ACR 70	19 (31.1%)	31 (44.3%)	17 (22.4%)	48 (36.9%)

[a] By assigned treatment group as of Week 52.
[b] Subjects are counted in the column through the last visit on that dose.

The MAH applies to add the following wording: "*Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively*". This wording is accepted by the CHMP.

DAS28 (CRP) Responders After Week 52 Through Week 104 (see Table Attachment 3.11 below)

Attachment 3.11 Number of DAS28 (using CRP) responders after Week 52 through Week 104; randomized subjects who received golimumab

	Golimumab			
	Placebo → 50 mg	50 mg Only	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab[a]	95	103	25	135
Subjects in response[b]				
Week 64				
n	91	97	25	127
Subjects in response	78 (85.7%)	89 (91.8%)	19 (76.0%)	110 (86.6%)
Week 76				
n	84	95	24	127
Subjects in response	78 (92.9%)	85 (89.5%)	19 (79.2%)	111 (87.4%)
Week 88				
n	82	92	34	126
Subjects in response	76 (92.7%)	81 (88.0%)	26 (76.5%)	111 (88.1%)
Week 100				
n	69	80	53	125
Subjects in response	61 (88.4%)	75 (93.8%)	46 (86.8%)	110 (88.0%)
Week 104				
n	58	68	72	124
Subjects in response	51 (87.9%)	68 (100.0%)	61 (84.7%)	111 (89.5%)

[a] By assigned treatment group as of Week 52.
[b] Subjects are counted in the column through the last visit on that dose.

The MAH applied to add the following wording: "*Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ responses were maintained through week 104*". This wording is accepted by the CHMP.

PASI 75 at week 104

PASI responses were analyzed in subjects with ≥ 3% BSA (body surface area) psoriasis skin involvement at baseline. See Table 11 for week 104 results.

Table 11 Number of subjects who achieved PASI 50, PASI 75, and PASI 90 response after Week 52 through Week 104; randomized subjects who received golimumab and who had a >= 3% BSA psoriasis skin involvement at baseline

	Golimumab			
	Placebo → 50 mg	50 mg Only	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab and who had a ≥ 3% BSA psoriasis skin involvement at baseline[a]	65	71	22	101
Subjects in response[b]				
Week 64				
n	65	69	22	99
PASI 50	52 (80.0%)	59 (85.5%)	19 (86.4%)	89 (89.9%)
PASI 75	42 (64.6%)	47 (68.1%)	14 (63.6%)	74 (74.7%)
PASI 90	24 (36.9%)	25 (36.2%)	9 (40.9%)	46 (46.5%)
Week 76				
n	63	68	22	98
PASI 50	51 (81.0%)	60 (88.2%)	18 (81.8%)	93 (94.9%)
PASI 75	39 (61.9%)	43 (63.2%)	14 (63.6%)	80 (81.6%)
PASI 90	24 (38.1%)	33 (48.5%)	6 (27.3%)	49 (50.0%)
Week 88				
n	57	65	31	98
PASI 50	44 (77.2%)	56 (86.2%)	25 (80.6%)	89 (90.8%)
PASI 75	38 (66.7%)	43 (66.2%)	22 (71.0%)	76 (77.6%)
PASI 90	24 (42.1%)	27 (41.5%)	11 (35.5%)	50 (51.0%)
Week 100				
n	49	55	43	95
PASI 50	41 (83.7%)	46 (83.6%)	37 (86.0%)	89 (93.7%)
PASI 75	34 (69.4%)	36 (65.5%)	27 (62.8%)	76 (80.0%)
PASI 90	23 (46.9%)	25 (45.5%)	21 (48.8%)	54 (56.8%)
Week 104				
n	43	48	56	96
PASI 50	37 (86.0%)	43 (89.6%)	46 (82.1%)	85 (88.5%)
PASI 75	31 (72.1%)	33 (68.8%)	35 (62.5%)	73 (76.0%)
PASI 90	23 (53.5%)	21 (43.8%)	25 (44.6%)	49 (51.0%)

[a] By assigned treatment group as of Week 52.
[b] Subjects are counted in the column through the last visit on that dose.

The MAH applies for the following wording: "*Of the 109 patients with > 3% BSA involvement at baseline who were randomised to Simponi 50 mg, 48 were still on this treatment at week 104. Of these 48 patients, 33 had a PASI 75 response. It is not agreed to include this level of data for a number of 'other secondary endpoints'*". This wording was not accepted by CHMP.

Health Assessment Questionnaire Responders Week 104

The proportion of subjects who achieved an improvement from baseline in HAQ of ≥ 0.25 and ≥ 0.30 at Week 52 and maintained this improvement from baseline in HAQ at Week 104 was summarized by treatment group (Table 12).

Table 12 Number of subjects who achieved a >= 0.25 unit improvement from baseline in HAQ score at Week 52, and maintained a >= 0.25 improvement from baseline at Week 104; randomized subjects who received golimumab

	Golimumab			
	Placebo → 50 mg	50 mg Only	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab and achieved a ≥ 0.25 unit improvement from baseline at Week 52	68	64	11	85
Subjects with ≥ 0.25 unit improvement from baseline at Week 104	59 (86.8%)	58 (90.6%)	11 (100.0%)	81 (95.3%)

SF-36

Table 14 Summary of change from baseline in SF-36 physical and mental component summary scores at Week 104; randomized subjects who received golimumab

	Golimumab			
	Placebo → 50 mg	50 mg Only	50 mg → 100 mg	100 mg
Randomized subjects who received golimumab	68	75	80	135
Physical component summary				
n	62	68	75	129
Mean ± SD	10.30 ± 11.464	9.98 ± 9.121	7.65 ± 11.078	9.30 ± 10.500
Median	9.60	8.25	6.40	8.60
IQ range	(1.20, 18.10)	(3.25, 16.40)	(-0.30, 15.40)	(3.10, 15.80)
Range	(-20.1, 36.9)	(-6.8, 33.5)	(-18.1, 33.8)	(-18.7, 35.2)
Mental component summary				
n	62	68	75	129
Mean ± SD	2.65 ± 11.544	4.79 ± 12.164	5.67 ± 11.572	5.10 ± 12.123
Median	1.45	2.90	4.30	3.40
IQ range	(-4.60, 9.40)	(-1.45, 11.65)	(-1.50, 13.70)	(-1.00, 11.20)
Range	(-24.6, 32.7)	(-25.4, 37.7)	(-25.3, 32.7)	(-32.3, 35.0)

The MAH applied for the addition of the following wording*: "Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS 28 and HAQ responses were maintained through week 104"*. These changes are accepted by the CHMP.

Conclusions on clinical efficacy

The joint damage claim is based on newly submitted X-ray data from and the long-term extension of study C0524T08. The effect of golimumab on progression of joint damage was assessed using the Modified van der Heijde-Sharpe, which is considered to be a valid instrument for assessment of X-ray data, and has been used in other applications for the same claim. The primary X-ray analysis was undertaken by comparing 24 weeks placebo and golimumab results. Thereafter, all placebo subjects were switched to active treatment. There was also an option for early escape after 16 weeks. The study was well conducted with only 17% of patient discontinuing during 104 weeks and with no major difference in withdrawal pattern with respect to amount or cause.

Although the progression rate was limited in the placebo group due to the short duration (24 weeks), statistically significant differences in favour of active treatment was seen for mean change in Modified van der Heijde-Sharp score as well as for percentage of patients with no progression between baseline and week 24 (78.8% vs 62.7% for golimumab and placebo respectively). Considering the low withdrawal rate with no differential withdrawal pattern and consistent results in sensitivity analyses, there is no reason to question the robustness of these results.

Concerning maintenance of effect an increasing positive effect on structural damage cannot be expected in study C0524T08 since all patients were given active treatment from week 24. At best a sustained difference between patients initially randomised to active treatment and placebo could be expected, and the percentage of patients with no progression between baseline and week 52 and week 104 was similar to the responder rate at week 24 for patients initially randomised to active treatment.

Although the data is too limited to fully evaluate the clinical long term relevance of the golimumab effects on structural damage in patients with psoriatic arthritis it can be concluded that a substantial number of patients could experience beneficial effects on joint damage progression. It is further considered that essential support can be gained from RA, where more knowledge about joint damage progression is available.

Symmetric PsA shows greatest resemblance with RA, and in subgroup analyses performed by the MAH significant effects was observed in this PsA subtype only. This is consistent with experience from other anti-TNF agents for which an effect in subjects with symmetrical disease has been shown, while relevant effects in subjects with asymmetrical disease have been less convincing. Thus the claim on positive effects on structural damage has been restricted to the polyarticular symmetrical subtypes of PsA.

The MAH also applies for changes to section 5.1 of the SPC to include a number of endpoints. These changes are agreed for all except PASI75 data, which was not accepted to be included by the CHMP.

Clinical safety

Introduction

The safety data presented in this submission focus on the 2-year cumulative safety data in study C0524T08. In addition, available safety data are presented from other studies in rheumatologic and non-rheumatologic indications through the end of those studies or completed data base locks (DBLs), including a 2-year cut off in ongoing Phase 3 studies with SC golimumab in RA (C0524T05, C0524T06, C0524T11), and AS (C0524T09). The 2-year data in RA (three of these studies) have been submitted and reviewed within a recently ended procedure; II-08. Thus, the focus below will be data from T08. All data presented below are through week 104.

Exposure:

In the Phase 3 PsA study with SC golimumab, there were 394 subjects treated with golimumab, with the vast majority (85.0%) of subjects treated for $\geq$104 weeks. Through Week 100/104, there were similar numbers of subjects exposed to golimumab 50 mg and golimumab 100 mg (248 subjects and 227 subjects, respectively) with a similar average number of administrations in both groups (18.2 and 18.5, respectively). Most subjects received golimumab by at least Week 24 (subjects could have entered early escape at Week 16 or crossed over to golimumab group from the placebo group before Week 24).

As a result of this study design, the average duration of follow up for subjects in the placebo group (19.6 weeks) was substantially shorter than the average duration of follow up for subjects in the golimumab treatment groups (75.1 weeks and 76.3 weeks for the golimumab 50 mg and 100 mg groups, respectively). This substantial difference in exposure to placebo and golimumab should be taken into consideration when interpreting the data.

All AEs:
AEs occurred in 61.1% of the placebo group, 78.2% of subjects in the golimumab 50 mg group and in 70.9% of subjects in the golimumab 100 mg group with similar types of AEs occurring with similar frequencies in the golimumab treatment groups. AEs were most frequently associated with the Infections and infestations system-organ class with upper respiratory tract infection being the most frequent infection occurring in 20.6% of the golimumab 50 mg group and 17.6% of the golimumab 100 mg group.

Deaths:
There were 2 deaths that both occurred in the golimumab 50 mg group. One subject died due to a metastatic small cell lung carcinoma, and the other subject died due to a climbing accident. The incidence per 100 subject-years follow up was 0.56 in the golimumab 50 mg group (confidence interval [CI]: 0.07, 2.02).

All SAEs:
SAEs occurred in: Placebo: 7.1%, Golimumab 50 mg: 6.5%, Golimumab 100 mg: 7.9%, Combined Golimumab: 8.6%. SAEs were most frequently associated with the Infections and infestations system organ class and occurred in 3.5% (4 subjects) of subjects in the placebo group, 0.8% (2 subjects) of subjects in the golimumab 50 mg group, 1.3% (3 subjects) of subjects in the golimumab 100 mg group, and 1.3% (5 subjects) in the combined golimumab group.

AEs leading to discontinuation:
AEs leading to discontinuation occurred in 4.4% of subjects in the golimumab 50 mg group and 5.3% of subjects in the golimumab 100 mg group. AEs leading to discontinuation of study agent occurred most frequently in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) system-organ class and occurred in 0.0% (0 subjects) of the placebo group, 1.2% (3 subjects) of the golimumab 50 mg group, and 2.2% (5 subjects) in the golimumab 100 mg group.

Serious infections:
Rerious infections were observed in 1.2% of subjects in the golimumab 50 mg group and 1.3% of subjects in the golimumab 100 mg group with similar types of serious infections occurring with similar frequencies across the golimumab treatment groups. See Table 15 below

Table 15 Number of subjects with 1 or more serious infections through Week 104 by MedDRA system-organ class and preferred term; treated subjects in PsA Phase 3 study

		Golimumab[a]		
	Placebo[b]	50 mg	100 mg	Combined
Treated subjects in PsA Phase 3 study[c]	113	248	227	394
Avg duration of follow-up (weeks)	19.6	75.1	76.3	91.3
Avg exposure (number of administrations)	4.6	18.2	18.5	22.1
Subjects with 1 or more serious infections	4 (3.5%)	3 (1.2%)	3 (1.3%)	6 (1.5%)
System-organ class/preferred term				
Infections and infestations	4 (3.5%)	2 (0.8%)	3 (1.3%)	5 (1.3%)
Abscess	0 (0.0%)	2 (0.8%)	0 (0.0%)	2 (0.5%)
Cellulitis	1 (0.9%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Histoplasmosis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Sepsis	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Pneumonia	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urosepsis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatobiliary disorders	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Cholecystitis acute	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Vascular disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.3%)
Thrombophlebitis superficial	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.3%)

[a] Prior to Week 104, received golimumab with or without MTX.
[b] Prior to Week 104, received placebo with or without MTX.
[c] C0524T08. Subjects may appear in more than one column.

Malignancies Through Week 100/104:

There were no subjects in the placebo group, 3 subjects in the golimumab 50 mg group, and 5 subjects in the golimumab 100 mg group with malignancies. See Table 16 below.

Table 16 Number of subjects with 1 or more malignancies through Week 104; treated subjects in PsA Phase 3 study

	Placebo[b]	Golimumab[a] 50 mg	Golimumab[a] 100 mg	Golimumab[a] Combined
Treated subjects in PsA Phase 3 study[c,d]	113	248	227	394
Type of malignancy				
Lymphoma				
Total subject-years of follow-up	43	358	333	692
Median subject-years of follow-up	0.3	1.7	2.0	2.0
Observed number of subjects with event	0	0	0	0
Incidence per 100 subject-years	0.00	0.00	0.00	0.00
95% confidence interval[e]	(0.00, 7.04)	(0.00, 0.84)	(0.00, 0.90)	(0.00, 0.43)
Nonmelanoma skin cancers				
Total subject-years of follow-up	43	358	332	690
Median subject-years of follow-up	0.3	1.6	2.0	2.0
Observed number of subjects with event	0	1	3	4
Incidence per 100 subject-years	0.00	0.28	0.90	0.58
95% confidence interval[e]	(0.00, 7.04)	(0.01, 1.56)	(0.19, 2.64)	(0.16, 1.48)
Other malignancies				
Total subject-years of follow-up	43	358	333	691
Median subject-years of follow-up	0.3	1.7	2.0	2.0
Observed number of subjects with event	0	2	2	4
Incidence per 100 subject-years	0.00	0.56	0.60	0.58
95% confidence interval[e]	(0.00, 7.04)	(0.07, 2.02)	(0.07, 2.17)	(0.16, 1.48)
All malignancies				
Total subject-years of follow-up	43	358	332	689
Median subject-years of follow-up	0.3	1.6	2.0	2.0
Observed number of subjects with event	0	3	5	8
Incidence per 100 subject-years	0.00	0.84	1.51	1.16
95% confidence interval[e]	(0.00, 7.04)	(0.17, 2.45)	(0.49, 3.52)	(0.50, 2.29)

[a] Received golimumab with or without MTX.
[b] Received placebo with or without MTX.
[c] C0524T08.
[d] Subjects may appear in more than one column.
[e] Confidence intervals based on an exact method.

According to the CHMP, the large difference in duration of follow up should be considered, and thus these data are difficult to interpret. There were some cases of malignancy reported during the study, and a relation to treatment cannot be excluded. The CHMP is of the opinion that the product information and RMP address risk for malignancy adequately.

Injection-site reactions:
See Table below for an overview of number of injections and of injection reactions. No subject had a severe injection-site reaction.

Table 17 Summary of injection-site reactions through Week 104 by intensity; treated subjects in PsA Phase 3 study

		Golimumab[a]		
	Placebo[b]	50 mg	100 mg	Combined
Treated subjects in PsA Phase 3 study[c]	113	248	227	394
Avg number of injections	9.3	34.0	33.4	40.6
Subjects with 1 or more injection-site reactions	3 (2.7%)	19 (7.7%)	16 (7.0%)	35 (8.9%)
Subjects with 1 or more mild injection-site reactions	3 (2.7%)	19 (7.7%)	16 (7.0%)	35 (8.9%)
Subjects with 1 or more moderate injection-site reactions	0 (0.0%)	0 (0.0%)	2 (0.9%)	2 (0.5%)
Subjects with 1 or more severe injection-site reactions	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total number of injections	1046	8432	7575	16007
Injections with injection-site reactions	8 (0.8%)	63 (0.7%)	46 (0.6%)	109 (0.7%)
Mild	8 (0.8%)	63 (0.7%)	44 (0.6%)	107 (0.7%)
Moderate	0 (0.0%)	0 (0.0%)	2 (0.0%)	2 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Prior to Week 104, received golimumab with or without MTX.
[b] Prior to Week 104, received placebo with or without MTX.
[c] C0524T08. Subjects may appear in more than one column.

The CHMP confirmed that the data on injection reactions do not raise any concerns.

Serum sickness-like and anaphylactic reactions:
There were no serum sickness-like reactions or anaphylactic reactions.

Clinically important hepatobiliary events:
There was 1 subject (0.9%) in the placebo group and 1 subject (0.3%) in the combined golimumab group who developed 1 or more clinically important hepatobiliary AEs. The same subject (C0524T08 5209-80378) had a clinically important hepatobiliary AE while receiving golimumab 50 mg and another clinically important hepatobiliary AE when receiving golimumab 100 mg.

Markedly abnormal hematology or chemistry values:
There were few subjects with > 1 markedly abnormal haematology value through Week 104. The most frequent changes included decreased absolute neutrophils which occurred in 0.0% (0 subjects) of the placebo group, 0.8% (2 subjects) of the golimumab 50 mg group, and 3.8% (8 subjects) of the golimumab 100 mg group. There were also a few subjects with > 1 markedly abnormal chemistry value through Week 104. The most frequent changes included elevated ALT/SGPT which occurred in 3.6% (4 subjects) of the placebo group, 2.8% (7 subjects) of the golimumab 50 mg group, 1.4% (3 subjects) of the golimumab 100 mg group, and 2.3% (9 subjects) of the combined golimumab group.

Safety in Special Groups and Situations:
There were no meaningful differences observed with regard to safety based on baseline demographic characteristics (sex, weight, and race).

Incidence of Antibodies to Golimumab
The incidence of antibodies to golimumab through Week 104 is summarized in Table 18 below.

	Golimumab			
	50 mg[a]	50 mg → 100 mg[a]	100 mg	Combined
Subjects treated with golimumab[b]	167	81	146	394
Subjects with appropriate samples[c]	162	81	145	388
Subjects positive for antibodies to golimumab at any time[d,e]	7 (4.3%)	6 (7.4%)	8 (5.5%)	21 (5.4%)
Titers				
1:20	2	0	1	3
1:40	2	0	1	3
1:80	1	1	3	5
1:160	1	1	1	3
1:320	0	2	1	3
1:640	0	0	1	1
1:2560	1	2	0	3
Subjects negative for antibodies to golimumab[d,f]	155 (95.7%)	75 (92.6%)	137 (94.5%)	367 (94.6%)

[a] Includes subjects randomized to placebo.
[b] Each subject may only appear in one treatment group column.
[c] Subjects with appropriate samples had 1 or more samples obtained after their first study agent administration.
[d] Denominator is subjects with appropriate samples.
[e] Includes all subjects who had at least 1 positive sample at any time.
[f] Excludes subjects who were positive at any time and includes subjects whose samples may contain golimumab.

Of the 8 subjects who were positive for antibodies to golimumab at Week 52, 1 subject (12.5%) remained positive at Week 100 and had an increased antibody titer. Seven subjects changed from positive at Week 52 to negative for antibodies at Week 100. All subjects who were negative for antibodies to golimumab at Week 52 remained negative at Week 100.

Conclusions on clinical safety

The MAH submitted long-term extension data from the open label study T08, which included data up to 2 years of treatment of PsA patients with golimumab. The already established safety profile of golimumab is confirmed. Infections, including some serious and severe, occurred in association with golimumab treatment. There were in total 8 malignancies reported; all in golimumab treated subjects. The large difference in duration of follow up between placebo (19.6 weeks) and golimumab (75-76 weeks) groups should be considered. Thus, these data are difficult to interpret, but a relation to treatment cannot be excluded. The CHMP is of the opinion that the product information and RMP address risk for malignancy adequately.

In summary, the safety profile of golimumab is comparable with that already well established for anti-TNF agents. No new signals are identified.

Risk Management Plan

A new version of the EU Risk Management Plan (v.4.O, dated 19 November 2010) has been submitted within the submission of the PSUR#3 on December 2, 2010 (eCTD sequence 0068). This document covers both the PSUR as well as this variation application. Based on the data included in this submission, no changes to the RMP are proposed. This is considered acceptable by the CHMP.

Benefit-risk assessment

The MAH applies to add wording to the PsA indication, to reflect data on structural joint damage measured by X-ray. Changes to section 5.1 are also proposed. These claims are based on newly submitted X-ray data from the long-term extension of study C0524T08. This study was the basis for the initial approval of PsA.

The effect of golimumab on progression of joint damage was assessed using the Modified van der Heijde-Sharpe, which is considered to be a valid instrument for assessment of X-ray data, and has been used in other applications for the same claim. The primary X-ray analysis was undertaken by comparing 24 weeks placebo and golimumab results. Thereafter, all placebo subjects were switched to active treatment. There was also an option for early escape after 16 weeks. The study was well conducted with only 17% of patient discontinuing during 104 weeks and with no major difference in withdrawal pattern with respect to amount or cause.

Although the progression rate was limited in the placebo group due to the short duration (24 weeks), statistically significant differences in favour of active treatment was seen for mean change in Modified van der Heijde-Sharp score as well as for percentage of patients with no progression between baseline and week 24 (78.8% vs 62.7% for golimumab and placebo respectively). Considering the low withdrawal rate with no differential withdrawal pattern and consistent results in sensitivity analyses, there is no reason to question the robustness of these results.

Concerning maintenance of effect an increasing positive effect on structural damage cannot be expected in study C0524T08 since all patients were given active treatment from week 24. At best a sustained difference between patients initially randomised to active treatment and placebo could be expected, and the percentage of patients with no progression between baseline and week 52 and week 104 was similar to the responder rate at week 24 for patients initially randomised to active treatment.

Although the data is too limited to fully evaluate the clinical long term relevance of the golimumab effects on structural damage in patients with psoriatic arthritis it can be concluded that a substantial number of patients could experience beneficial effects on joint damage progression. It is further considered that essential support can be gained from RA, where more knowledge about joint damage progression is available.

Symmetric PsA shows greatest resemblance with RA, and in subgroup analyses performed by the MAH significant effects was observed in this PsA subtype only. This is consistent with experience from other anti-TNF agents for which an effect in subjects with symmetrical disease has been shown, while relevant effects in subjects with asymmetrical disease have been less convincing. Thus the claim on positive effects on structural damage has been restricted to the polyarticular symmetrical subtypes of PsA.

The MAH also applies for changes to section 5.1 of the SPC to include number of endpoints. The inclusion of PASI75 data was not agreed by the CHMP.

With respect to safety, the MAH has submitted long-term extension data from the open label study T08, which included data up to 2 years of treatment of PsA patients with golimumab. The already established safety profile of golimumab is confirmed. Infections, including some serious and severe, occurred in association with golimumab treatment. There were in total 8 malignancies reported; all in golimumab treated subjects. The large difference in duration of follow up between placebo (19.6 weeks) and golimumab (75-76 weeks) groups should be considered. Thus, these data are difficult to interpret, but a relation to treatment cannot be excluded. The product information and RMP address risk for malignancy, as well as the other well-established safety concerns related to treatment with an anti-TNF agent adequately. Thus, the safety profile of golimumab is comparable with that already well established for anti-TNF agents. No new signals are identified.

The benefit-risk balance for Simponi is positive in this new indication. Furthermore, the submitted data do not modify the current benefit-risk balance.