6 Review of Efficacy

Major Efficacy Results for RA

In Study 6, the combination groups (golimumab and MTX), compared to the MTX control group had a greater proportion of ACR 20 responders at Week 14 and in Study 11, the golimumab groups, compared to the placebo group, had a greater proportion of ACR 20 responders at Week 14. The results of these primary efficacy endpoints in Studies 6 and 11 were statistically significant. In Study 5, the combination groups, compared to the MTX control group, had a greater proportion of ACR 50 responders at Week 24 using the randomized population, the primary statistical population, but these results were not statistically significant (p-value was 0.053 for the combined combination groups vs. the MTX control). These results are consistent with the efficacy of the 3 approved TNF inhibitors in this RA subpopulation — patients who are MTX-naive (see Section 6.1.9 Additional Efficacy Issues/Analyses – RA). In Study 5, the combination groups, compared to the MTX control group, had a greater proportion of ACR 20 responders at Week 24 (a secondary efficacy endpoint).

In Study 6 the golimumab combination groups, compared to the MTX control, had greater proportions of ACR 50, ACR 70, and ACR-N responders at Week 14 and in Study 11, the golimumab groups, compared to placebo, had greater proportions of ACR 50, ACR 70, and ACR-N responders at Week 14. In Studies 6 and 11, the ACR 20, 50, and 70 responses were maintained at Week 24.

In Studies 5 and 6, the golimumab combination groups, compared to the MTX control group, had greater median improvements in the 7 ACR components and in Study 11, the golimumab groups, compared to the placebo control, had greater median improvements in the 7 ACR components.

There was no clear evidence of dose response of the low and high dose golimumab groups in the 3 Phase 3 RA trials. In Studies 5 and 6, the high dose combination groups had similar responses as the low dose combination groups and in Study 11, the golimumab100 and golimumab50 groups appeared to have similar responses.

The golimumab monotherapy groups did not clearly demonstrate greater efficacy than the MTX monotherapy groups in Studies 5 and 6. In Study 5, the golimumab monotherapy group, compared to the MTX monotherapy group, had similar proportion of ACR 50 responders at Week 24 and in Study 6, the golimumab monotherapy group, compared to the MTX control, had a greater proportion of ACR 20 responders at Week 14, but these results were not statistically significant.

Improvement in physical function was evaluated in the 3 RA Phase 3 trials evaluating HAQ responders — the proportion of patients with a change in HAQ from baseline at Week 24 greater or equal to 0.22 [a minimally clinically important difference (MCID) in RA]. In Studies 5 and 6, the combination groups, compared to the MTX control groups, had greater proportions of HAQ responders at Week 24 (71% vs. 63% in Study 5 and 65% vs. 35% in Study 6, using FDA's conservative imputation) and in Study 11, the golimumab groups, compared to the placebo groups, had greater proportions of HAQ responders at Week 24 (47% vs. 28%, using FDA's conservative imputation).

Overall, the results of the 3 Phase 3 RA trials support the efficacy of the combination of SC golimumab with MTX for the treatment of signs and symptoms and the improvement of physical function in patients with moderately to severely active RA. There have been no comparative trials of golimumab to the other TNF inhibitors in the treatment of the signs and symptoms of RA. Although cross-study comparisons have major limitations, golimumab appeared to have similar efficacy as the other TNF inhibitors in the 3 distinct RA populations.

Major Efficacy Results for PsA

The low and high dose golimumab groups demonstrated statistically significantly greater proportions of ACR 20 responders than the placebo group (i.e., the sign and symptoms primary endpoint) with absolute treatment margins between 36 to 42%. The low and high dose golimumab groups had greater proportions of ACR 50 and 70 responders than the placebo group. These treatment effects were maintained or increased at Week 24. There was no evidence of dose response. The low and high dose golimumab groups had greater percentage change in the 7 ACR components compared to the placebo group.

In a subgroup efficacy analysis, the golimumab groups, compared to the placebo group, had a greater proportion of ACR 20 responders at Week 14 for patients who received MTX and for patients who did not receive MTX. This supports the efficacy of golimumab with or without concomitant MTX in the treatment of the signs and symptoms of PsA.

Improvement in physical function was evaluated in the PsA trial evaluating HAQ responders — the proportion of patients with a change in HAQ from baseline at Week 24 greater or equal to 0.3 [a minimally clinically important difference (MCID) in PsA]. The golimumab groups, compared to the placebo group, had greater proportions of HAQ responders at Week 24 (48% vs. 22%, using the FDA's conservative analysis).

Overall, the results of the PsA trial support the efficacy of SC golimumab with or without concomitant MTX for the treatment of signs and symptoms and the improvement of physical function in patients with moderately to severely active PsA. There have been no comparative trials of golimumab to the other TNF inhibitors in the treatment of the signs and symptoms of PsA. In cross-study comparisons, golimumab appeared to have similar efficacy in the treatment of signs and symptoms of PsA as the other TNF inhibitors in PsA.

Major Efficacy Results for AS

The low and high dose golimumab groups demonstrated statistically significantly greater proportions of ASAS 20 responders (i.e., the primary endpoint) than the placebo group with absolute treatment margins between 37 to 38%. The low and high dose golimumab groups, compared to the placebo group, also had greater proportions of ASAS 40 responders. These treatment effects were maintained at Week 24. There was no clear evidence of a dose response between the low and high dose golimumab groups. The low and high dose golimumab groups, compared to the placebo group, had greater improvements in the 4 ASAS components at Week 14.

Overall, the results of the AS trial support the efficacy of SC golimumab for the treatment of signs and symptoms in patients with moderately to severely active AS. There have been no comparative trials of golimumab to the other TNF inhibitors in the treatment of the signs and symptoms of AS. In cross-study comparisons, golimumab appeared to have similar efficacy in the treatment of signs and symptoms of AS as the other TNF inhibitors.

6.1 Indication – [redacted] Rheumatoid Arthritis (RA) b(4)

Centocor proposes the following RA indication: "SIMPONI, in combination with methotrexate, is indicated for [redacted] adult patients with moderate to severely active rheumatoid arthritis. [redacted] b(4)

6.1.1 Methods – RA

Studies 5, 6, and 11 served as the critical trials for the evaluation of the efficacy of SC golimumab in the treatment of signs and symptoms of RA. These trials were adequate and well-controlled (double-blind, controlled), had acceptable endpoints, and they included three distinct RA populations with different mean durations of disease.

6.1.2 Demographics and Baseline Characteristics – RA

Table 6.1 displays the baseline demographics in the 3 RA Phase 3 trials (i.e., Studies 5, 6, and 11). The mean age and gender were similar in the 3 RA trials and is typical of an RA population — middle-aged women.

All three trials had a similar proportion of patients from Europe, Australia, Canada, and New Zealand. Study 11 had a greater proportion of patients in the United States and Studies 5 and 6 had a greater proportion of patients from Latin America, Mexico, and Asia. Study 11, compared to Studies 5 and 6, had a greater proportion of Caucasians and lower proportion of Asians. These differences were probably due to the regional differences in the trials — there is a greater proportion of Asians in Asian countries compared to the United States. Study 11, compared to Studies 5 and 6, had a greater mean weight. These differences were probably due to the regional differences — Americans have a greater mean weight than people in Latin America, Mexico, and Asia. Baseline demographics were balanced between treatment groups within each trial (data not shown). For the baseline demographic results for each treatment group, see the individual study reports in Section 9.4.

Table 6.1: Baseline demographics in the RA Phase 3 trials (i.e., Studies 5, 6, and 11)[1]

		Study 5 (MTX-naive) (n=637)	Study 6 (inadequate MTX response) (n=444)	Study 11 (prior use of TNF inhibitor) (n=461)
Age	Mean (SD)	50 (12) years	50 (11) years	54 (12) years
Sex	Female	83%	81%	80%
	Male	17%	19%	20%
Race	Caucasian	72%	77%	87%
	Asian	18%	15%	2%
	Black	2%	1%	5%
	Other	7%	7%	5%
Weight	Mean (SD)	158 (42) lbs	161 (40) lbs	174 (46) lbs
Height	Mean (SD)	64 (4) inches	65 (4) inches	65 (4) inches
Region[2]	Europe, Australia, Canada, & New Zealand	44%	52%	42%
	Latin America & Mexico	19%	18%	0%
	United States	18%	16%	58%
	Asia	18%	15%	0%

1 ITT was the pre-specified statistical population (all randomized patients) for the efficacy analyses
2 European countries in Study 5 (i.e., Austria, Belgium, Hungary, Italy, Poland, Russia, Spain, Ukraine, and the UK); in Study 6 (i.e., Germany, Hungary, and Poland); and in Study 11 (i.e., Austria, Finland, Germany, the Netherlands, Spain, and UK). Latin American countries in Study 5 (i.e., Argentina and Chile) and Study 6 (i.e., Argentina, Chile). Study 6 included sites in Mexico. Asian countries in Study 5 (i.e., India, Malaysia, the Philippines, Singapore, Korea, Taiwan, and Thailand) and in Study 6 (i.e., South Korea, Taiwan).
Reference: Adapted from Final Study Report for Study 5, Table 12, Page 84-85; the Final Study Report for Study 6, Table 7, Page 79; and the Final Study Report for Study 11, Table 9, Pages 76-77; JMP demographic datasets for Studies 5, 6, and 11.

Table 6.2 displays the baseline disease characteristics of the patients in the RA trials (i.e., Studies 5, 6, and 11).

The mean baseline RA disease durations in Studies 5, 6, and 11 were about 4, 8, and 12 years, respectively; the proportion of patients with prior joint procedures or injections were 18%, 32%, and 41%, respectively; and the proportion of patients with baseline rheumatoid nodules was 9%, 15%, and 22%, respectively. Thus, it appears that the eligibility criteria were able to select appropriate study populations. Patients in Study 5 (i.e., MTX-naive) had the shortest durations of disease, the least likely to have a prior joint procedure or injection and the least likely to have rheumatoid nodules. Patients in Study 11 (i.e., prior use of a TNF-inhibitor) had the longest disease durations, were most likely to have a prior joint procedure or injection, and were the most likely to have rheumatoid nodules.

All three trials had similar baseline disease activity whether using DAS28 (CRP) values or ACR core component values. Baseline disease activity and characteristics were also balanced between treatment groups within each trial (data not shown). For the baseline disease activity results for each treatment group see the individual study reports in Section 9.4.

Table 6.2: Baseline disease characteristics in the RA trials (i.e., Studies 5, 6, and 11)[1]

		Study 5 (MTX-naive) (n=637)	Study 6 (inadequate MTX response) (n=444)	Study 11 (prior use of TNF inhibitor) (n=461)
Disease duration, mean		3.5 years	8.3 years	11.8 years
Prior joint procedure or injections		18%	32%	41%
Duration of morning stiffness, mean		2.9 hours	2.0 hours	2.9 hours
Received MTX in the past		0%	100%	95%
Extra-Articular Manifestations	Rheumatoid nodules	9%	15%	22%
	Sicca syndrome	6%	10%	10%
	Peripheral neuropathy	2%	1%	4%
	Interstitial lung fibrosis	1%	1%	1%
	Vasculitis	1%	0.3%	0.2%
Mean ACR Core Components	# of swollen joints (0-66)	16	15	16
	# of tender joints (0-68)	28	26	30
	Patient's assessment of pain[2]	6	6	7
	Patient's assessment disease activity[2]	6	6	6
	Physician's assessment disease activity[2]	6	6	6
	HAQ disability index (0-3)	1.53	1.35	1.56
	CRP mg/dL (normal about < 0.5 mg/dL)	2.5	1.8	2.1
Other Characteristics	DAS28 (CRP) score, mean	5.1	4.9	5.2
	Positive anti-CCP antibodies	74%	80%	72%
	Positive rheumatoid factor	80%	84%	73%

1 ITT was the pre-specified statistical population (all randomized patients) for the efficacy analyses.
2 Scored on a VAS 0-10 cm
Reference: Adapted from Final Study Report for Study 5, Table 13, Pages 87-88, Table 14, Pages 89-90; Table 1.13, Pages 235-236; from Final Study Report for Study 6; Table 1.18, Page 251-252; Table 8, Pages 82-83; Table 1.19, Pages 253-254; and from Final Study Report for Study 11, Table 10, Pages 78-79; Table 1.13, Page 260-261; Table 11, Page 80

Table 6.3 presents the percent of patients who received NSAIDs, corticosteroids, and/or DMARDs prior to enrollment in the RA trials (i.e., Studies 5, 6, and 11).

Almost all patients received NSAIDs prior to enrollment in the three RA trials. A greater proportion of patients in Studies 6 and 11, compared to patients in Study 5, received MTX (95 to 100% versus 0%) and systemic corticosteroids (88 to 89% versus 67%) prior to enrollment. Patients in studies with longer disease durations had had greater use of DMARDs prior to enrollment than patients in studies with shorter disease durations. In Studies 5, 6, and 11, 0%, 0%, and 100% of the patients received at least one dose of a TNF inhibitor prior to enrollment, respectively. This is consistent with the eligibility criteria in these studies.

Table 6.3: Percent of patients who received NSAIDs, corticosteroids, and/or DMARDs prior to enrollment in the RA trials (i.e., Studies 5, 6, and 11)[1]

	Study 5 (MTX-naive) (n=637)	Study 6 (inadequate MTX response) (n=444)	Study 11 (prior use of TNF inhibitor) (n=461)
Mean disease duration	3.5 years	8.3 years	11.8 years
NSAIDs	98%	98%	97%
Systemic corticosteroids	67%	88%	89%
TNF inhibitor[2]	0%	0%	100%
rituximab[3]	0%	0%	0%
abatacept	0%	0%	0%
Patients who took ≥ 1 DMARD	55%	75%	99%
MTX	0%	100%	95%
sulfasalazine	30%	40%	35%
hydroxychloroquine	22%	32%	45%
leflunomide	8%	19%	38%
gold preparations	4%	14%	28%
azathioprine	1%	3%	11%
cyclosporine	1%	10%	7%

1 ITT statistical population (patients randomized regardless of whether or not they receive the assigned treatment) was the primary statistical population for the efficacy analyses
2 In Studies 5 and 6, patients were not allowed to have ever received a TNF inhibitor; in Study 11 patients had to have received at least one dose of a TNF inhibitor in the past to be enrolled.
3 In Studies 5, 6, and 11, patients who received rituximab in the past were excluded from participation.
Reference: Adapted from Final Study Report for Study 5, Table 1.19, Page 249-250; Table 1.20, Pages 251-255; from the Final Study Report for Study 6, Table 1.22, Page 260, Table 1.23, Page 261-265; from the Final Study Report for Study 11, Table 1.19, Page 273; Table 1.20, Pages 274-277; Table 1.25, Page 293. Also adapted from the concomitant medications datasets in Studies 5, 6, and 11.

Table 6.4 displays the proportion of patients who received NSAIDs, corticosteroids, MTX, HCQ, and/or SSZ at baseline in the RA trials (i.e., Studies 5, 6, and 11). Patients were considered to be taking these medications at baseline if they had been used both prior to **and** after the first study agent administration. The data in Table 6.4 differs from the data in Table 6.3 which displays the proportion of patients who received treatments for RA prior to enrollment. Also Table 6.4 displays the percent of patients who received oral steroids; whereas, Table 6.3 displays the percent of patients who received systemic steroids. In Studies 5 and 6, patients were not allowed to be receiving HCQ or SSZ at baseline; whereas, in Study 11 patients were allowed to be receiving HCQ or SSZ at baseline.

In the RA trials, 61% to 85% of patients were receiving NSAIDs at baseline and 52% to 70% were receiving steroids at baseline. In Studies 6 and 11, 66% to 70% of patients were receiving MTX at baseline and in Study 5 no patients were receiving MTX. There was minimal use of hydroxychloroquine or sulfasalazine at baseline in the three trials.

The protocols for the 3 RA trials stated that patients were to remain on stable doses of low-dose oral corticosteroids and/or NSAIDs during the 24-week controlled period. In the 3 RA trials, the proportion of patients who received oral corticosteroids and NSAIDs at baseline was similar to the proportion of patients who received these medications at Weeks 14 and 24 during the trials (see Table 9.1.17, Table 9.2.14, and Table 9.3.15 in the individual study reports for Studies 5, 6, and 11,

respectively). For patients who received oral corticosteroids or NSAIDs, the mean dose of these medications was similar at Weeks 14 and 24 (see Table 9.1.17, Table 9.2.14, and Table 9.3.15 in the individual study reports for Studies 5, 6, and 11, respectively). Therefore, the use of oral corticosteroids and NSAIDs **at baseline** (use prior to and after the first study agent) was similar to the use of these medications during the 24 week controlled periods.

Table 6.4: Percent of who received NSAIDs, corticosteroids, MTX, HCQ, and/or SSZ <u>at baseline</u> in the RA trials (i.e., Studies 5, 6, and 11)[1]

	Study 5 (MTX-naive) (n=637)	Study 6 (inadequate MTX response) (n=444)	Study 11 (prior use of TNF inhibitor) (n=461)
Mean disease duration	3.5 years	8.3 years	11.8 years
NSAIDs at baseline	85%	85%	61%
Oral corticosteroids at baseline	52%	70%	53%
For patients who received oral steroids, mean prednisone dose or equivalent[3]	7 mg	7 mg	7 mg
MTX at baseline	0%	70%	66%
For patients who received MTX, mean dose	0	17 mg	17 mg
HCQ at baseline	0%	0%	8%
SSZ at baseline	0.2%	0%	5%

1 ITT was the pre-specified statistical population for the efficacy analyses (all randomized patients)
Reference: Adapted from Final Study Report for Study 5, Table 1.21, Page 256; from the Final Study Report for Study 6, Table 10, Page 86; and from the Final Study Report for Study 11, Table 13, Page 85.

6.1.3 Patient Disposition - RA

Table 6.5 delineates the patient disposition through Week 24 in the RA trials (i.e., Studies 5, 6, and 11). In Table 6.5 the combination groups of golimumab and MTX are combined (for more details, see Tables 9.1.12, 9.2.9, and 9.3.9 in the individual study reports for Studies 5, 6, and 11, respectively, in Section 9.4).

In Study 6, a lower proportion of patients in the combination groups compared to the golimumab monotherapy group and the MTX monotherapy group entered early escape. In Study 11, a lower proportion of patients in the golimumab ± DMARDs groups, compared to the placebo ± DMARDs group, entered early escape.

Across all 3 trials, there were a similar proportion of patients who had an adverse event leading to discontinuation (DAE). For a discussion of the DAEs in Studies 5, 6, and 11 see Tables 9.1.23, 9.2.21, and 9.3.24, respectively, in the individual study reports in Section 9.4.

Table 6.5: Patient disposition through Week 24 in Studies, 5, 6, and 11

	Study 5 (MTX-naive)			Study 6 (inadequate MTX response)			Study 11 (prior use of TNF inhibitor)	
	MTX	G100	G50/G100[1] & MTX	MTX	G100	G50/G100[1] & MTX	Placebo ± DMARDs	G50/G100[2] ± DMARDs
Patients randomized[3], n	160	159	318	133	133	178	155	306
Patients who received ≥ 1 dose of SC agent[4], n (%)	160 (100%)	157 (99%)	317 (100%)	133 (100%)	133 (100%)	178 (100%)	155 (100%)	304 (99%)
Patients who entered the escape phase at Week 16[5]	N/A	N/A	N/A	31%	27%	16%	47%	27%
Patients who discontinued SC study agent	6%	6%	6%	8%	7%	5%	20%	9%
Adverse event	1%	1%	4%	5%	5%	4%	7%	2%
Other	3%	3%	1%	1%	1%	1%	6%	2%
Lost to follow-up	2%	0%	1%	1%	0%	1%	0%	1%
Unsatisfactory therapeutic effect	1%	2%	0%	2%	1%	0%	7%	4%

G50 is golimumab 50 mg SC given once every 4 weeks and G100 is golimumab 100 mg SC given once every 4 weeks; MTX is 20 mg of oral MTX given once weekly (starting dose of MTX 10 mg once weekly and then escalation by Week 20 to 20 mg once weekly)

1 Combined combination groups (G50& MTX and G100 & MTX)

2 Combined G50 and G100 groups

3 Randomized patients (regardless of whether or not they receive the assigned treatment) was the ITT population and was the primary statistical population for the efficacy analyses.

4 Patients who received ≥ 1 dose of SC agent was the treated statistical population and was the primary statistical population for all the safety analyses and clinical pharmacology analyses. Two patients in the G100 monotherapy group and one patient in the low dose combination group were randomized and never treated because they all withdrew consent.

5 In Studies 6 and 11, any patient who had < 20% improvement from baseline in both swollen and tender joint counts was supposed to enter early escape in a double-blinded fashion. Study 5 had early escape beyond Week 24 (i.e., at Week 28).

Reference: Adapted from Final Study Report for Study 5, Table 4, Page 69; Table 1.1, Page 182; Table 1.2, Page 183; Table 4, Page 69; Table 5, Page 70; Table 6, Page 72; Study 11 Disposition Datasets.

6.1.4 Analysis of Sign and Symptom Endpoints – RA

Table 6.6 displays the major signs and symptoms efficacy endpoints at Weeks 14 and 24 in the 3 Phase 3 RA trials (Studies 5, 6, and 11) including the pre-specified sign and symptom primary efficacy endpoints (i.e., the proportion of ACR50 responders at Week 24 in Study 5 and the proportion of ACR20 responders at Week 14 in Studies 6 and 11). The 4 treatment groups in Study 5, the 4 treatment groups in Study 6, and the 3 treatment groups in Study 11 were all different and cannot be directly compared across the trials. The MTX monotherapy groups in Studies 5 and 6 were different because in Study 5 patients were naive to MTX prior to enrollment and in Study 6 patients were receiving MTX and had an inadequate response. Additionally, in the three trials, the patient populations were heterogeneous (e.g., patients had different durations of RA disease, received a different number of DMARDs in the past, and patients received different concomitant medications for RA during the trial) — see Section 6.1.2 (Demographics and Baseline Characteristics – RA) for more details on the heterogeneity of the RA populations in the three trials. Given the heterogeneity of the RA populations and treatment groups in the 3 trials, the results were not pooled.

In 2 of the 3 RA trials, Studies 6 and 11, golimumab was superior to the control groups for the primary efficacy endpoint, and this difference was statistically significant. In each of these trials, the primary

endpoint was the proportion of ACR 20 responders at Week 14, and the primary comparison was the combined combination groups vs. the MTX monotherapy group in Study 6 and the combined golimumab groups vs. the control group in Study 11. Comparisons of the individual golimumab doses also demonstrated superiority to the control groups for both the 50 and 100 mg golimumab doses. In both trials, the absolute treatment effect size was approximately 20% higher responses in the combined golimumab groups vs. the control groups. These studies also demonstrated treatment effects favoring golimumab with respect to the secondary endpoints of ACR 50, ACR 70, and ACR-N responders at Week 14. Treatment effects appeared to remain high over time, with similar proportions of ACR 20, 50, and 70 responders in the golimumab treatment groups at Week 24.

In Study 5, the combination groups, compared to the MTX control group, had a greater proportion of ACR 50 responders at Week 24 using the randomized population, the primary statistical population, but these results were not statistically significant. Using a post-hoc statistical population (all treated patients) in Study 5, the low dose combination group (golimumab50 and MTX) was superior to the MTX group in the proportion of ACR 50 responders. The difference between the randomized and treated populations for this analysis was one randomized patient in the low dose combination group that was not treated. In addition, in Study 5 the combination groups, compared to the MTX control group, had a greater proportion of ACR 20 responders at Week 24. Although this study failed to demonstrate the efficacy of golimumab for the primary endpoint, results of this study are consistent with trials of other TNF inhibitors, which do not demonstrate superiority to optimized MTX in the MTX-naïve RA population.

There was no clear evidence of dose response in the RA trials. In Study 11, the golimumab100 group appeared to have similar response as the golimumab50 group and in Studies 5 and 6, the high dose combination groups had similar responses as the low dose combination groups.

The golimumab monotherapy groups did not clearly demonstrate greater efficacy than the MTX monotherapy groups in Studies 5 and 6. In Study 5, the golimumab monotherapy group had a similar proportion of ACR 50 responders at Week 24 compared to the MTX monotherapy group and in Study 6, the golimumab monotherapy group had a greater proportion of ACR 20 responders at Week 14 but this was not statistically significant.

Overall, the results of the RA trials support the efficacy of the combination of golimumab with MTX for the treatment of signs and symptoms of RA; however, treatment with golimumab at 100 mg did not appear to offer any additional efficacy over the 50 mg dose with respect to ACR responses.

Table 6.6: Major signs and symptoms efficacy endpoints at Weeks 14 and 24 in the 3 Phase 3 RA trials (Studies 5, 6, and 11)[1]

Study 11 (prior use TNF inhibitor)		Placebo ± DMARDs (n=155)	—	Golimumab50 ± DMARDs (n=153)	Golimumab100 ± DMARDs (n=153)	Combined Golimumab Groups (n=306)
ACR 20 responders	Week 14	18%	—	35%	38%	37%
	p-value (vs. MTX)	—	—	< 0.001	< 0.001	< 0.001
	Week 24	17%	—	34%	44%	39%
ACR 50 responders	Week 14	6%	—	16%	20%	18%
	Week 24	5%	—	18%	20%	19%
ACR 70 responders	Week 14	2%	—	10%	9%	10%
	Week 24	3%	—	12%	10%	11%
ACR-N Index, mean (SD)	Week 14	-17 (64)	—	10 (49)	6 (55)	8 (52)
	Week 24	-33 (96)	—	7 (50)	16 (44)	11 (47)
Study 6 (inadequate MTX response)		**MTX (n=133)**	**Golimumab100 (n=133)**	**Golimumab50 & MTX (n=89)**	**Golimumab100 & MTX (n=89)**	**Combined Combination Groups (n=178)**
ACR 20 responders	Week 14	33%	44%	55%	56%	56%
	p-value (vs. MTX)	—	0.059	0.001	< 0.001	< 0.001
	Week 24	28%	35%	60%	60%	60%
ACR 50 responders	Week 14	10%	20%	35%	29%	32%
	Week 24	14%	20%	37%	33%	35%
ACR 70 responders	Week 14	4%	8%	13%	9%	11%
	Week 24	5%	11%	20%	15%	17%
ACR-N Index, mean (SD)	Week 14	-10 (62)	-4 (78)	23 (46)	19 (51)	21 (48)
	Week 24	-17 (84)	-8 (83)	22 (58)	28 (38)	25 (49)
Study 5 (MTX naive)		**MTX (n=160)**	**Golimumab100 (n=159)**	**Golimumab50 & MTX (n=159)**	**Golimumab100 & MTX (n=159)**	**Combined Combination Groups (n=318)**
ACR 20 responders at Week 24[2]		49%	52%	62%	62%	62%
p-value (versus MTX)		—	0.677	0.028	0.028	0.011
ACR 50 responders at Week 24		29%	33%	40%	37%	38%
p-value (versus MTX)		—	0.521	0.042	0.177	0.053
ACR 70 responders at Week 24		16%	14%	24%	18%	21%
ACR-N Index at W24, mean (SD)		20 (48)	21 (47)	28 (70)	27 (51)	28 (61)

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks. For Study 5, MTX is 20 mg of oral MTX given once weekly (starting dose of MTX 10 mg and then escalation to 20 mg by Week 20). For Study 6, MTX is the background weekly oral MTX used prior to enrollment (15-25 mg). For Studies 5, 6, and 11 patients may have taken stable doses of concomitant MTX, corticosteroids (equivalent to ≤ 10 mg prednisone/day), and/or NSAIDs during the study. For Study 11, patients may have also taken stable doses of concomitant sulfasalazine, and/or hydroxychloroquine during the study.

1 The 3 studies are in order of greatest disease duration. In Studies 11, 6, and 5, RA patients had mean disease durations of approximately 12, 8, and 4 years, respectively. The pre-specified statistical population for all ACR responder efficacy analyses in Studies 5, 6, and 11 were all randomized patients. The primary efficacy endpoint in Study 5 was the proportion of patients that achieved an ACR 50 response at Week 24 and the primary efficacy endpoint in Studies 6 and 11 were the proportion of patients that achieved an ACR 20 response at Week 14. The pre-specified sign and symptom primary efficacy endpoints results for the trials are highlighted in yellow.

2 The proportion of patients with an ACR 20 response at Week 24 was 1 of 4 pre-specified secondary endpoints in Study 5 (however, there were no multiplicity adjustments).

Reference: Adapted from Final Study Report for Study 5, Table 17, Page 107, Table 18, Page 110, Table 3.5, Page 421; Table 18, Page 110; Table 3.16 Page 432; Table 3.21, Pages 442; and Table 3.26, Pages 447-448. Also adapted from Final Study Report for Study 6, Table 13, Page 107, Table 18, Page 115; Table 3.18, Page 445; Table 3.19, Page 446; Table 3.20, Page 447; Table 3.21, Page 448; Table 15, Page 111. Also adapted from Final Study Report for Study 11; Table 16, Page 100; Table 19, Page 105; Table 21, Page 107; Table 3.14, Page 452; Table 3.15, Page 453; Table 3.21, Page 464.

6.1.5 Analysis of Physical Function Endpoints – RA

As per the 1999 *Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis* Guidance (RA Guidance), the Agency has historically required at least 2 years of Health Assessment Questionnaire Disability Index (HAQ-DI) data to support an improvement in physical function claim in RA. At the time, the rationale for this was that effective treatments would have to prevent the joint damage associated with uncontrolled disease for an extended period of time in order to demonstrate a reduction in physical dysfunction that results from this damage. However, experience with other TNF inhibitors has since demonstrated that improvement in physical functioning occurs rapidly, and that much of physical dysfunction in RA is actually the result of uncontrolled inflammation. Therefore, an extended period of time, such as 2 years, is no longer considered necessary to demonstrate efficacy for this claim. To this end, Centocor has submitted controlled 24-week data on the HAQ-DI. The HAQ has been validated in RA and extensively used in RA clinical trials. Based on validation studies, the minimally clinically important difference (MCID) in RA patients has been identified as decreases greater than or equal to 0.22 units (based on group means). For a given individual, based on HAQ scoring, the MCID would be greater than or equal to 0.25 units of improvement.

Table 6.7 displays the proportion of patients with a change in HAQ from baseline at Week 24 that was greater than or equal to 0.25 in the three RA trials.

In the analysis submitted by Centocor, only observed data were utilized in calculating the proportion of responders. In order to corroborate this analysis using the intent-to-treat (ITT) population, FDA statistician Dr. Jonathan Norton imputed any missing patients as nonresponders. Both analyses demonstrated a higher proportion of patients in the golimumab treatment groups achieving a minimally clinically important improvement in the HAQ at Week 24, compared to controls. These analyses support the efficacy of SC golimumab for the improvement of physical function in RA. See Dr. Jonathan Norton's review for more details.

Table 6.7: Proportion with change in HAQ ≥ 0.25 at Week 24 in the RA trials (i.e., Studies 5, 6, and 11)

	Study 5 (MTX-naive)				Study 6 (inadequate response to MTX)				Study 11 (prior use of TNF inhibitor)		
	MTX	G100	G50 & MTX	G100 & MTX	MTX	G100	G50 & MTX	G100 & MTX	Placebo ± DMARDs	G50 ± DMARDs	G100 ± DMARDs
Randomized	160	159	159	159	133	133	89	89	155	153	153
Patients in HAQ analysis	150	146	150	150	127	128	88	86	131	142	140
Baseline HAQ (mean)	1.50	1.58	1.49	1.53	1.32	1.34	1.41	1.35	1.58	1.57	1.48
W24 HAQ (mean)	0.98	1.00	0.87	0.80	1.17	1.08	0.94	0.90	1.51	1.32	1.18
Δ from baseline at W24 (mean)	0.52	0.57	0.62	0.72	0.15	0.25	0.47	0.46	0.05	0.25	0.30
Proportion with Δ change from baseline at W24 ≥ 0.25 (Centocor[1])	67%	68%	73%	79%	39%	45%	68%	72%	35%	51%	54%
Proportion with Δ change from baseline at W24 ≥ 0.25 (FDA[2])	63%	61%	68%	73%	35%	42%	65%	64%	28%	44%	49%

1 In Centocor's analysis, no treatment failure rules were applied and there was no missing data imputation. In Patients in the MTX and golimumab monotherapy and the low dose combination groups in Study 6, non-missing Week 24 HAQ scores were replaced with Week 16 HAQ scores. Patients in the placebo and golimumab50 groups in Study 11, non-missing Week 24 HAQ scores were replaced with Week 16 HAQ scores.

2 In the FDA's conservative imputation (performed by Dr. Jonathan Norton, the statistical reviewer) patients are considered non-responders if treatment failure or there was discontinuation of SC study agent by Week 24.

Reference: Adapted from HAQ dataset using JMP in Studies 5, 6, and 11; final study report for Study 6, Table 3.25, Page 456

6.1.6 Subpopulations – RA

See the individual study reports for Studies 5, 6, and 11 for the subgroup efficacy analyses by primary efficacy endpoint by demographics, disease duration, RF status, and baseline medication use subgroups. Treatment with golimumab appeared to confer a benefit for all subgroups analyzed.

Because golimumab is being proposed for approval as a fixed dose, an analysis of efficacy by weight quartiles (≤ 61 kg, > 61 to ≤ 71 kg, > 71 to ≤ 84.5 kg, and > 84.5 kg) was requested by the Agency for this BLA in order to assess whether higher weight patients might experience less efficacy (and whether lower weight patients might experience more adverse events) from the fixed dose. In Studies 5 and 6, there was no differential response based on patient weight in the combination golimumab groups compared to the MTX groups. In Study 11, patients of higher body weight had a lower response to golimumab regardless of dose, although an apparent treatment benefit did remain (see Figure 9.3.22 in the individual study report for Study 11). Thus overall, there does not appear to be a dose-by-weight efficacy interaction, and a fixed dose, as proposed, appears reasonable. See Table 7.6.2 in Section 7.6.3 (Drug-Demographic Interactions) for the subgroup safety analyses by weight.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations – RA

Centocor studied 8 different golimumab treatment regimens in their Phase 3 RA trials [all patients may have received stable doses of corticosteroids (equivalent to ≤ 10 mg prednisone/day), and/or NSAIDs during the study]:

1. SC golimumab 100 mg once every 4 weeks (golimumab100) and weekly oral MTX (in Study 5)
2. SC golimumab 50 mg once every 4 weeks (golimumab50) and weekly oral MTX (in Study 5)
3. golimumab100 monotherapy (in Study 5)
4. golimumab100 monotherapy after stopping background MTX (in Study 6)
5. Addition of golimumab100 to background MTX (in Study 6)
6. Addition of golimumab50 to background MTX (in Study 6)
7. golimumab100 (in Study 11) with possible background MTX, sulfasalazine, and/or hydroxychloroquine.
8. golimumab50 (in Study 11) with possible background MTX, sulfasalazine, and/or hydroxychloroquine.

There was no evidence of clear dose response in the Phase 3 RA trials. Treatment effects with golimumab50 were similar to treatment effects with golimumab100 in all efficacy comparisons (see Table 6.6). Efficacy results also demonstrated that treatment with golimumab in combination with MTX was consistently superior to golimumab monotherapy (see Table 6.6).

As a result, Centocor proposes golimumab be approved for the treatment of RA at the dose and regimen of 50 mg SC once monthly in combination with MTX, and this reviewer concurs that this dose and regimen appear to be supported by the submitted data. Centocor does not propose the use of the higher golimumab dose or the use of golimumab monotherapy in RA. Centocor does not propose dose regimen modification or titration for individual subgroups.

The clinical trial protocols specified a dosing frequency of once every 4 weeks with allowed variation ± 3 to 7 days. To simplify use in clinical practice, Centocor proposes to label the dosing frequency for once a month, although this might result in slight variability in the duration between dose administrations. In order to explore whether this variability might result in a clinically meaningful difference from the results observed in the clinical trials, additional analyses were performed (see Table 6.8 for the duration between the SC agent administrations through Week 24 in the 3 Phase 3 RA trials).

About 86% of the patients in the RA trials received at least one dose of SC agent after 29 days and about 28% of all SC administrations occurred after 29 days. Monthly dosing is acceptable, given that the protocols allowed for a 3-7 day variation in dosing frequency and a significant number of patients received SC golimumab around 30.4 days (the mean number of days in each month). Finally, once monthly dosing is much more convenient for patients with RA and for health care providers than once every 4 week dosing.

Table 6.8: Duration between of SC administration agent through Week 24 in the 3 RA Phase 3 trials

		Placebo	Combined Golimumab	Total
Treated patients		448	1203	1537
Percent of patients with maximum duration between SC administrations	0-28 days	18%	17%	14%
	29-31 days	34%	32%	33%
	> 31 days	48%	51%	53%
Number of administration intervals		2224	6373	8597
# of SC administrations intervals Percent of SC administrations between	0-28 days	73%	72%	72%
	29-31 days	16%	16%	16%
	> 31 days	12%	13%	12%

Reference: Adapted from monthly-admin-golimumab report, Table 1, Page 3.

6.1.8 Persistence of Efficacy, Tolerance, and Efficacy by Immunogenicity – RA

Treatment with golimumab appeared to result in similar proportions of ACR responders over time, from baseline to Week 24 (see Section 6.1.4 Analysis of Sign and Symptom Endpoints – RA for more details).

Table 6.9 summarizes efficacy with respect to ACR 20 or ACR 50 responses by subgroups of patients with and without human anti-human antibodies (HAHA) as a result of golimumab treatment in the 3 RA Phase 3 trials.

Very few patients developed anti-golimumab HAHAs in the RA Phase 3 trials (31 of 766, or 4%, of those tested), making it difficult to draw any definitive conclusions. Based on this very small sample size, the ACR 20 response at Week 24 for patients with positive HAHA appeared to be lower than for patients with either negative HAHA or undetectable HAHA (45% vs. 55%). Similarly, the ACR 50 response at Week 24 for patients with positive HAHA was lower than for patients with either negative HAHA or undetectable HAHA (13% vs. 33%). These data suggest immunogenicity overall is not a significant concern with golimumab treatment, but are not adequate to be able to make definitive statements regarding efficacy by immunogenicity interactions in labeling.

Table 6.9: Patients with ACR 20 or ACR 50 observed response at Week 24 for patients with positive HAHA who received golimumab in the RA Phase 3 trials

	Study 5	Study 6	Study 11	Pooled RA Phase 3 Trials
Golimumab-treated patients	474	311	304	1089
Treated patients who received golimumab with appropriate samples	315	236	215	766
Patients who received golimumab with HAHA at anytime, n (%)	19 (6%)	5 (2%)	7 (3%)	31 (4%)
ACR 20 responders, n (%)	11 (58%)	3 (60%)	0 (0%)	14 (45%)[1]
ACR 50 responders, n (%)	3 (16%)	1 (20%)	0 (0%)	4 (13%)[2]

1 In comparison, the patients who received golimumab with appropriate samples who were either negative for HAHA or had undetectable HAHA had 55% ACR 20 responders.

2 In comparison, the patients who received golimumab with appropriate samples who were either negative for HAHA or had undetectable HAHA had 33% ACR 50 responders.

Reference: Summary of clinical efficacy for RA, Table 19, Page 63.

6.1.9 Additional Efficacy Issues/Analyses – RA

It is important to determine if golimumab has similar efficacy to the 3 other approved TNF inhibitors in the treatment of the signs of symptoms of RA (infliximab, etanercept, and adalimumab). However, there have been no comparative trials of the efficacy of golimumab to another TNF inhibitor in the treatment of the signs of symptoms of RA. Study 11, which included patients who received at least one dose of a biologic TNF inhibitor, was not adequately designed to support comparative efficacy claims because patients may have stopped the use of a TNF inhibitor for multiple reasons including financial cost or improvement in disease.

Cross-study comparisons have multiple limitations including heterogeneous patient populations (e.g., different severity of disease, concomitant medications), different pre-specified endpoints, different time points of efficacy measurements, and different study conduct. Nonetheless, while these might preclude definitive conclusions, cross study comparisons could be useful to provide a general idea about golimumab's performance compared to other TNF inhibitors, and are thus provided here. In an attempt to compare similar populations, trials of TNF inhibitors were separated into 3 groups: patients with active RA who were naive to MTX (Table 6.10), patients with active RA despite MTX (Table 6.11), and patients with refractory active RA (Table 6.12). These tables present the proportion of patients with ACR 20 response at various time points.

As summarized in Table 6.10 below, in patients with active RA who were MTX naive, the TNF inhibitor and MTX combination group had a greater proportion of ACR 20 responders than the MTX monotherapy group with absolute treatment effect sizes ranging from 7 to 13%. In these cross-study comparisons golimumab appeared to have similar efficacy as the other approved TNF inhibitors.

As summarized in Table 6.11 below, in patients with active RA despite MTX, the TNF inhibitor and MTX combination groups had greater proportions of ACR 20 responders than the MTX monotherapy group with absolute treatment effect sizes ranging from 30 to 54%. Golimumab and MTX combination groups had greater proportions of ACR 20 responders than the MTX monotherapy group with treatment effects ranging from 22 to 23%. In these cross-study comparisons, golimumab appeared to have slightly lower efficacy than the other TNF inhibitors.

As summarized in Table 6.12 below, in patients with more refractory active RA, the TNF inhibitor and MTX combination group had a greater proportion of ACR 20 responders than the MTX monotherapy group with absolute treatment effect sizes ranging from 18 to 20%. In these cross-study comparisons golimumab appeared to have similar efficacy as the other approved TNF inhibitors.

Overall, these analyses suggest that golimumab may have similar efficacy as the other TNF inhibitors in the three different RA populations.

Table 6.10: ACR 20 responders in TNF inhibitor trials in patients with active RA who were MTX naive[1]

Golimumab Study 5				
	MTX (n=160)	**Golimumab100 Monotherapy (n=159)**	**Golimumab50 & MTX (n=159)**	**Golimumab100 & MTX (n=159)**
ACR 20 Response at Week 24	**49%**	**52%**	**62%**	**62%**
Infliximab Study RA-2				
	MTX (n=274)	**IV Infliximab 3 mg/kg q 8 weeks[2] & MTX (n=351)**	**IV Infliximab 6 mg/kg q 8 weeks[2] & MTX (n=355)**	
ACR 20 Response at Week 54	**54%**	**62%**	**66%**	
Adalimumab Study RA-5				
	MTX (n=257)	**SC Adalimumab 40 mg every other week Monotherapy (n=274)**	**SC Adalimumab 40 mg every other week & MTX (n=268)**	
ACR 20 Response at Week 52	**63%**	**54%**	**73%**	
Etanercept Study RA-3				
	MTX (n=217)	**SC Etanercept 10 mg two times a week & MTX (n=208)**	**SC Etanercept 25 mg two times a week & MTX (n=207)**	
ACR 20 Response at Month 6	**58%**	**N/A**	**65%**	

1 From the approved labels and publically available medical officer reviews
2 Patients who received infliximab, initially received IV infusions of infliximab at Weeks 0, 2, and 6.

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Table 6.11: ACR 20 responders in TNF inhibitor trials in patients with active RA despite MTX[1]

Golimumab Study 6					
	MTX (n=133)	**Golimumab100 (n=133)**	**Golimumab50 & MTX (n=89)**	**Golimumab100 & MTX (n=89)**	
ACR 20 Response at Week 24	**33%**	**44%**	**55%**	**56%**	
Infliximab Study RA-1					
	MTX (n=88)	**IV Infliximab 3 mg/kg q 8 weeks[2] & MTX (n=86)**	**IV Infliximab 3 mg/kg q 4 weeks[2] & MTX (n=86)**	**IV Infliximab 10 mg/kg q 8 weeks[2] & MTX (n=87)**	**IV Infliximab 10 mg/kg q 4 weeks[2] & MTX (n=81)**
ACR 20 Response at Week 30	**20%**	**50%**	**50%**	**52%**	**58%**
Adalimumab Study RA-1					
	MTX (n=60)	**SC Adalimumab 20 mg every other week & MTX (n=67)**	**SC Adalimumab 40 mg every other week & MTX (n=63)**	**SC Adalimumab 80 mg every other week & MTX (n=70)**	
ACR 20 Response at Week 24	**13%**	**48%**	**67%**	**66%**	
Adalimumab Study RA-3					
	MTX (n=200)	**SC Adalimumab 20 mg/week & MTX (n=212)**	**SC Adalimumab 40 mg every other week & MTX (n=207)**		
ACR 20 Response at Week 24	**30%**	**61%**	**63%**		
Etanercept Study RA-2					
	MTX (n=30)	**SC Etanercept 25 mg two times a week & MTX (n=59)**			
ACR response at Month 6	**27%**	**71%**			

1 From the approved labels and publically available medical officer reviews
2 Patients who received infliximab, initially received IV infusions of infliximab at Weeks 0, 2, and 6.

Table 6.12: ACR 20 responders in TNF inhibitor trials in patients with active RA with refractory disease[1]

Golimumab Study 11			
	Placebo ± DMARDs (n=155)	**Golimumab50 ± DMARDs (n=153)**	**Golimumab100 ± DMARDs (n=153)**
ACR 20 Response at Week 24	**18%**	**35%**	**38%**
Adalimumab Study RA-4			
	Background DMARDs (n=315)	**SC Adalimumab 40 mg every other week & background DMARDs (n=315)**	
ACR 20 Response at Week 24	**35%**	**53%**	

1 From the approved labels and publically available medical officer reviews

6.2 Indication – Treatment of [redacted] Psoriatic Arthritis (PsA)

b(4)

Centocor proposes the following PsA indication: "SIMPONI, alone or in combination with methotrexate, is indicated for [redacted] active arthritis in adult patients with psoriatic arthritis."

6.2.1 Methods – PsA

Study 8 served as the critical trial for the evaluation of the efficacy of SC golimumab in the treatment of signs and symptoms of PsA. This trial was well-controlled and had acceptable endpoints. One trial in PsA was determined to be sufficient to support the efficacy of SC golimumab in the treatment of PsA if the efficacy of SC golimumab was demonstrated in RA, a similar inflammatory autoimmune disease with destructive effects on the joints. Since there was one trial in PsA, the entire efficacy results are evaluated in this section.

6.2.2 Demographics and Baseline Characteristics - PsA

Table 6.13 displays the baseline demographics in the PsA trial (i.e., Study 8).

Demographics were similar in the three treatment groups. The age and gender distribution in Study 8 were similar to the typical psoriatic population (middle aged with a slightly higher proportion of men compared to women). The overwhelming predominance of the Caucasian race reflects both the study geographics (i.e., most of the patients lived in Europe) and the typical population afflicted by PsA.

Table 6.13: Baseline demographics in the PsA trial (i.e., Study 8)[1]

		Placebo ± MTX (n=113)	Golimumab50 ± MTX (n=146)	Golimumab100 ± MTX (n=146)
Age	Mean (SD)	47 (11) years	46 (11) years	48 (11) years
Sex	Female	39%	39%	41%
	Male	61%	61%	59%
Race	Caucasian	97%	97%	97%
	Asian	1%	2%	2%
	Black	1%	0%	1%
	Other	1%	1%	0%
Weight	Mean (SD)	86 (18) kg	84 (21) kg	87 (19) kg
Height	Mean (SD)	171 (9) cm	170 (9) cm	169 (10) cm
Region[2]	Europe and Canada	79%	77%	77%
	United States	21%	23%	23%

1 ITT was the pre-specified statistical population (all randomized patients) for the efficacy analyses

2 European countries in Study 8 included Belgium, Poland, Spain, and the United Kingdom.

Reference: Adapted from Final Study Report for Study 8 Table 12, Pages 86-87; also adapted from JMP demographics dataset from Study 8.

Table 6.14 displays the baseline disease characteristics in the PsA trial (i.e., Study 8).

There were no significant differences in the baseline disease characteristics in the three treatment groups in Study 8. In Study 8, the mean PsA duration was 7.5 years, the mean duration of morning stiffness was 2.1 hours, 48% of patients received MTX at baseline, 34% had dactylitis, and 77% had enthesitis. All the patients had baseline psoriasis (i.e. the eligibility criteria in Study 8 stated that all patients need to "have active plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter").

The placebo group, compared to the golimumab groups, had a greater proportion of the polyarticular form of PsA and a lower proportion of the asymmetric peripheral arthritis form of PsA. The polyarticular form, compared to the oligoarticular form, has been associated with greater disease progression. Since the golimumab groups demonstrated a large treatment effect size which far exceeds the difference in the proportion of patients with polyarticular disease between the treatment arms, it is unlikely that this imbalance would change the overall results favoring golimumab (see Section 6.2.4 for the efficacy results from Study 8).

The three treatment groups had similar baseline PsA disease activity [i.e., similar ACR core component scores and DAS28 (CRP) measurements]. The mean numbers of baseline swollen and tender joints were 13 and 23, respectively.

Table 6.14: Baseline disease characteristics in the PsA trial (i.e., Study 8)

		Placebo ± MTX (n=113)	Golimumab50 ± MTX (n=146)	Golimumab100 ± MTX (n=146)
PsA duration, mean (SD)		7.6 (8) years	7.2 (7) years	7.7 (8) years
Morning stiffness duration, mean (SD)		2.2 (4) hours	2.1 (4) hours	2.0 (4) hours
Received MTX		48%	49%	47%
Had dactylitis		34%	34%	34%
Had enthesitis		78%	75%	79%
Had psoriasis		100%	100%	100%
Psoriasis duration, mean (SD)		19 (13) years	18 (12) years	18 (13) years
Had ≥ 3% body surface area with psoriasis		70%	75%	74%
PsA subtypes	Polyarticular arthritis with no rheumatoid nodules	51%	43%	38%
	Asymmetric peripheral arthritis	24%	30%	34%
	DIP joint arthritis	14%	16%	15%
	Spondylitis (peripheral arthritis)	11%	10%	12%
	Arthritis mutilans	0%	1%	1%
ACR Core Components (median)	# of swollen joints (0-66)	10	11	10
	# of tender joints (0-68)	18	19	18
	Patient's assessment of pain[1]	5	6	6
	Disease activity (patient)[1]	5	5	5
	Disease activity (physician)[1]	5	5	5
	HAQ disability index (0-3)	1.00	1.00	1.13
	CRP mg/dL	0.6	0.6	0.6
# of swollen joints (0-66), mean (SD)		13 (10)	14 (11)	12 (8)
# of tender joints (0-68), mean (SD)		22 (15)	24 (17)	23 (16)
DAS28 (CRP), median		4.2	4.4	4.2

1 VAS 0-10

Reference: Adapted from Final Study Report for Study 8, Table 13, Page 89; Table 14, Pages 90-92, Attachment 1.10, Pages 231-232

Table 6.15 displays the proportion of patients who received DMARDs, immunosuppressives, corticosteroids, NSAIDs, alefacept, and/or efalizumab prior to enrollment in the PsA trial (i.e., Study 8). Patients who received any biologic anti-TNF product (e.g., infliximab, etanercept, adalimumab), rituximab, natalizumab, or a cytotoxic agent (e.g., chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents) were excluded from participation in Study 8.

There were no significant differences in the proportions of patients in the three treatment groups who received DMARDs, immunosuppressive products, steroids, NSAIDs, alefacept, or efalizumab in the past. In Study 8, 78%, 69%, 30%, 7%, 18%, 40%, and 97% of the patients received a DMARD, MTX, sulfasalazine, hydroxychloroquine, an immunosuppressive product, a systemic steroid, and an NSAID in the past, respectively. No patient received a TNF inhibitor prior to enrollment in Study 8 (i.e., any patient who received a TNF inhibitor in the past was excluded from participation in Study 8).

Table 6.15: Percent of patients who received DMARDs, immunosuppressives, corticosteroids, NSAIDs, alefacept, and/or efalizumab prior to enrollment in Study 8[1]

	Placebo ± MTX (n=113)	Golimumab50 ± MTX (n=146)	Golimumab100 ± MTX (n=146)
Received TNF inhibitor[2]	**0%**	**0%**	**0%**
Received ≥ 1 DMARD	**75%**	**75%**	**82%**
MTX	67%	66%	73%
Sulfasalazine	25%	31%	34%
Hydroxychloroquine	11%	6%	6%
Leflunomide	6%	1%	4%
Gold preparations	2%	4%	3%
Chloroquine	2%	1%	2%
Received ≥ 1 immunosuppressive	**15%**	**18%**	**20%**
Cyclosporine	10%	14%	16%
Azathioprine	4%	0%	1%
Received systemic corticosteroids	**41%**	**39%**	**41%**
Received NSAIDs	**99%**	**96%**	**97%**
Received alefacept[3]	**5%**	**4%**	**9%**
Received efalizumab[3]	**0%**	**0%**	**1%**

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; Patients may have received ≤ 25 mg of weekly MTX.

1 All randomized patients (all randomized patients in Study 8 were treated)

2 Patients who received any dose of a biologic TNF inhibitor in the past were excluded from enrollment in Study 8.

3 According to the protocol for Study 8, there was a 3 month wash-out period for receiving alefacept or efalizumab prior to study initiation. No patient received alefacept or efalizumab within three months of study initiation.

Reference: Adapted from Final Study Report for Study 8, Table 1.16, Page 246; Table 1.17, Page 247-248.

Table 6.16 displays the use of MTX, steroids, and/or NSAIDs at baseline in Study 8. A medication was considered to be used at baseline if it had been used both prior to **and** after administration of the first study agent.

There were no significant differences in the proportions of patients who received MTX, steroids, and/or NSAIDs at baseline. In Study 8, 48%, 16%, and 76% of the patients received MTX, steroids, and NSAIDs at baseline, respectively.

The proportions of patients who received concomitant MTX during the 24 week controlled period in the placebo, golimumab50, golimumab100 groups were 50%, 51%, and 49%, respectively. The proportions of patients who received MTX at baseline and during the 24 week period were similar. Also the proportions of patients who received NSAIDs and/or oral steroids at baseline, at Week 14, and at Week 24 were similar in the treatment groups. The mean daily dose of oral steroids at baseline, at Week 14, and at Week 24 was similar in the three groups.

Table 6.16: Use of MTX, corticosteroids, and/or NSAIDs at baseline in Study 8[1]

	Placebo ± MTX (n=113)	Golimumab50 ± MTX (n=146)	Golimumab100 ± MTX (n=146)
Received MTX at baseline	48%	49%	47%
For patients who received MTX, mean (SD) weekly dose	15 (4) mg	15 (5) mg	16 (5) mg
Received oral steroids at baseline	17%	13%	19%
For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	6 (2) mg	8 (2) mg	6 (2) mg
Received NSAIDs at baseline	78%	75%	75%

1 Patients may have taken stable doses of concomitant MTX equivalent to ≤ 25 mg once weekly, NSAIDs, and/or corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks. All randomized patients were treated in Study 8.
Reference: Adapted from Final Study Report for Study 8, Table 15, Page 96

6.2.3 Patient Disposition - PsA

Table 6.17 presents the patient disposition through Week 24 in Study 8.

A greater proportion of patients in the placebo group, compared to the golimumab groups, entered early escape. There was no significant difference in the proportion of patients who entered early escape in the low and high dose golimumab groups, indicating no significant dose response.

A lower proportion of patients in the golimumab groups, compared to the placebo group, discontinued the SC study agent and had an adverse event leading to discontinuation (DAE).

Table 6.17: Patient disposition through Week 24 in Study 8

	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX
Randomized[1], n	**113**	**146**	**146**
Received ≥ 1 dose of SC agent[2], n	**113**	**146**	**146**
Entered the escape phase at Week 16[3], %	**45%**	**19%**	**17%**
Discontinued SC study agent, %	**9%**	**5%**	**1%**
Adverse event, %	**4%**	**1%**	**1%**
Other, %	**3%**	**2%**	**0%**
Lost to follow-up, %	**1%**	**1%**	**0%**
Unsatisfactory therapeutic effect, %	**2%**	**1%**	**0%**

1. ITT Population included patients who were randomized regardless of whether or not they received the assigned treatment. The ITT population was used for the efficacy analyses.
2. Treated Population included patients who received at least one SC study agent administration. The treated population was used for the clinical pharmacology and safety analyses.
3. At Week 16, any patient who had < 10% improvement from baseline in both swollen and tender joint counts entered early escape in a double-blinded fashion.

Adapted from the Final Study Report for Study 8, Table 7, Page 75; Table 8, Page 77; also adapted from the Disposition Dataset for Study 8

6.2.4 Analysis of Sign and Symptom Endpoints – PsA

Table 6.18 displays the major signs and symptoms endpoints in the PsA trial (i.e., Study 8) including the results of the first primary efficacy endpoint (i.e., the proportion of patients who had an ACR 20 response at Week 24, using the randomized population). The results of the second primary endpoint in Study 8 (i.e., the change from baseline in total modified vdH-S score, modified for the purpose of PsA, for hands and feet at Week 24) were not submitted in this BLA.

b(4)

The low and high dose golimumab groups had greater proportions of ACR 20 responders than the placebo group (i.e., the first primary endpoint). The absolute treatment effect size for these statistically significant results between the high and low dose golimumab groups and the placebo group ranged from 36 to 42%.

The low and high dose golimumab groups had greater proportions of ACR 50 and 70 responders than the placebo group. These treatment effects were maintained or increased at Week 24.

The baseline PsA disease activity, as measured by the DAS28 (CRP), was similar in the three treatment groups. The low and high dose golimumab groups had a greater improvement in DAS28 (CRP) at Week 24 than did the placebo group, supporting the efficacy of the golimumab groups for the signs and symptoms of PsA.

Table 6.18: Major sign and symptom efficacy endpoints at Weeks 14 and 24 in Study 8

		Placebo ± MTX	Golimumab50 ± MTX	Golimumab100 ± MTX	Combined Golimumab Groups ± MTX
Randomized patients[1]		113	146	146	292
ACR 20 responders[2]	Week 14	9%	51%	45%	48%
	p-value vs. placebo	—	< 0.001	< 0.001	< 0.001
	Week 24[3]	12%	52%	61%	57%
ACR 50 responders	Week 14	2%	30%	28%	29%
	Week 24[4]	4%	32%	38%	35%
ACR 70 responders	Week 14	1%	12%	17%	15%
	Week 24[4]	1%	19%	21%	20%
ACR-N Index, mean (SD)	Week 14	-36 (67)	16 (53)	15 (55)	15 (54)
	Week 24	-38 (71)	14 (62)	31 (49)	23 (56)
Patients with W24 DAS28 (CRP)		97	134	137	271
DAS28 (CRP)[5], mean	Baseline	4.4	4.4	4.3	4.4
	Week 24	4.3	3.0	2.7	2.9
	Change	0.1	1.4	1.6	1.5

Patients may have taken stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks

1 Randomized patients was the primary statistical population for the efficacy analyses in Study 8.

2 ACR 20 responders at Week 14 was the first co-primary efficacy endpoint in Study 8.

3 ACR 20 responders at Week 24 was 1 of 4 pre-specified secondary endpoints without multiplicity adjustments in Study 8.

4 For the Week 24 ACR 50 and ACR 70 responder analyses, if patients met early escape criteria at Week 16 for the placebo and golimumab50 groups, the ACR component value at Week 24 was replaced with the corresponding component value at Week 16.

5 The DAS 28 (CRP) is an assessment of disease activity and it includes tender joints (maximum is 28), swollen joints (maximum is 28), CRP, and patient's assessment of disease activity. For the DAS28 (CRP) score, treatment failure rules were not applied and there was no missing data imputation. For patients who met early escape criteria at Week 16 for the placebo and golimumab50 groups, non-missing DAS component values at Week 24 were replaced with the corresponding values at Week 16.

Reference: Adapted from Final Study Report for Study 8; Table 18, Page 116; Table 19, Page 118; Table 23, Page 123; Attachment 3.18, Page 412; Attachment 3.23, Pages 418-419; also adapted from VISRA dataset for Study 8.

Table 6.19 presents the change from baseline in the 7 ACR components at Week 14 in Study 8. Golimumab treatment was associated with improvements in all ACR core variables, and produced greater improvements in all core variables compared to the placebo group. There was no evidence of a dose response for the ACR components; effects of golimumab50 were similar to effects of golimumab100.

Table 6.19: Change from baseline in the 7 ACR components at Week 14 in Study 8[1]

		Placebo ± MTX	Golimumab50 ± MTX	Golimumab100 ± MTX
Number of swollen joints (range is 0-66)	n with measurement	104	142	145
	Median # of swollen joints at baseline	10	11	10
	Median # of swollen joints at W14	10	4	4
	Percent change from baseline at W14	8%	60%	63%
Number of tender joints (range is 0-68)	n with measurement	104	142	145
	Median # of tender joints at baseline	18	19	18
	Median # of tender joints at W14	16	7	9
	Percent change from baseline at W14	0%	54%	43%
Patient's assessment of pain (VAS 0-10 cm)	n with measurement	102	139	140
	Median pain at baseline	5	6	6
	Median pain at W14	6	3	3
	Percent change from baseline at W14	-1%	48%	45%
Patient's assessment of disease activity (VAS 0-10 cm)	n with measurement	102	139	140
	Median disease activity at baseline	5	5	5
	Median disease activity at W14	5	3	3
	Percent change from baseline at W14	2%	49%	44%
Physician's assessment of disease activity (VAS 0-10 cm)	n with measurement	104	141	145
	Median disease activity at baseline	5	5	5
	Median disease activity at W14	5	2	2
	Percent change from baseline at W14	7%	59%	59%
HAQ disability index (0-3)	n with measurement	105	140	141
	Median HAQ at baseline	1.00	1.00	1.13
	Median HAQ at W14	1.00	0.50	0.63
	Percent change from baseline at W14	0%	28%	33%
CRP (mg/dL)	n with measurement	103	140	142
	CRP at baseline	0.6	0.6	0.6
	Median CRP at W14	0.7	0.3	0.3
	Percent change from baseline at W14	0%	40%	40%

1 These endpoints were included in the 140 other pre-specified endpoints related to signs and symptoms (no multiplicity adjustments). Patients may have taken stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks

Reference: Adapted from Final Study Report for Study 8, Table 3.13, Pages 402-403, also the VISRA JMP dataset for Study 8.

Table 6.20 displays the percent of patients with no dactylitis at Week 14 and the percent change from baseline in the dactylitis score at Week 14 in Study 8. Also Table 6.20 displays the percent of patients with no enthesitis at Week 14 and the percent change from baseline in the enthesitis score at Week 14 in Study 8.

Dactylitis and enthesitis are important and unique features of PsA that are not captured by the ACR response criteria, and thus were considered important secondary endpoints to support the efficacy of golimumab in PsA. The low and high dose golimumab groups, compared to the placebo group, had a greater improvement from baseline at Week 14 in the dactylitis score. A greater percent of patients with baseline dactylitis in the low and high dose golimumab groups, compared to the placebo group, had no dactylitis at Week 14. A slightly greater percent of patients without baseline dactylitis in the low and high dose golimumab groups, compared to the placebo group, remained free from dactylitis at Week 14.

The low and high dose golimumab groups, compared to the placebo group, had a greater improvement from baseline at Week 14 in the enthesitis score. A greater percent of patients with baseline enthesitis in the low and high dose golimumab groups, compared to the placebo group, had no enthesitis at Week 14. A slightly greater percent of patients without baseline enthesitis in the low and high dose golimumab groups, compared to the placebo group, remained free from enthesitis at Week 14.

Overall these results support the efficacy of golimumab in treating these other important manifestations of PsA and are consistent with the primary efficacy results.

Table 6.20: Dactylitis and enthesitis in Study 8[1]

		Placebo ± MTX (n=113)[2]	Golimumab50 ± MTX (n=146)[2]	Golimumab100 ± MTX (n=146)[2]
Patients with baseline dactylitis	Number of patients with dactylitis at baseline	33	48	49
	Patients with no digits with dactylitis at W14[3]	39%	40%	57%
	Median percent change from baseline in dactylitis score at W14[4]	0%	76%	100%
Patients without baseline dactylitis	Number of patients without dactylitis at baseline	72	94	96
	Patients with no digits with dactylitis at W14[3]	90%	98%	96%
Patients with baseline enthesitis	Number of patients with enthesitis at baseline	85	105	114
	Patients with no digits with enthesitis at W14[3]	18%	30%	26%
	Median percent change from baseline in enthesitis score at W14[4]	0%	50%	50%
Patients without baseline enthesitis	Number of patients without enthesitis at baseline	20	37	31
	Patients with no digits with enthesitis at W14[3]	75%	86%	86%

1 The dactylitis score ranged from 0 to 60 [each of the 20 digits was scored on a 0 (no dactylitis) to 3 (severe dactylitis)] scale. The enthesitis score was based on the modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) which assesses 15 sites. These 15 sites are evaluated for the presence (1) or absence (0) of tenderness so the range of the modified MASES score is 0-15.
2 Randomized patients in Study 8.
3 These were post-hoc analyses
4 These endpoints were 2 of 140 other sign and symptom endpoints in Study 8 without multiplicity adjustments.
Reference: Adapted from Final Study Report for Study 8, Table 3.26, Page 423, Table 3.27, Page 424; Table 3.28, Page 425; Table 3.30, Page 427; Table 3.31, Page 428; Table 3.32, Page 429.

6.2.5 Analysis of Physical Function Endpoints – PsA

Analogous to the situation with RA, the Agency has historically granted claims of improvement in physical function in PsA based on 2-year data using the HAQ, which has also been validated in PsA. As with RA, the Division now considers shorter duration controlled data to be adequate to grant this claim in PsA. One major difference between PsA and RA with respect to the HAQ is that validation studies have demonstrated that a slightly greater improvement is required to constitute the MCID; in PsA the MCID is an improvement of at least 0.3 units.

Table 6.21 displays the proportion of patients with a change in HAQ from baseline at Week 24 that was greater than or equal to 0.3 in the one PsA Phase 3 trial (Study 8). Dr. Joan Buenconsejo, the statistical reviewer, conducted an analysis using a conservative imputation of the proportion of patients with a change from baseline in HAQ $\geq$ 0.3 at Week 24 and her analysis had similar results as Centocor's analysis (see Dr. Joan Buenconsejo's review for more details).