The golimumab groups, compared to the placebo group, had greater proportions of HAQ responders at Week 24 in Study 8. These analyses support the efficacy of SC golimumab for the improvement of physical function in PsA.

Table 6.21: Proportion of patients with change from baseline in HAQ ≥ 0.3 (MCID) at Week 24 in the PsA trial (i.e., Study 8)

		Placebo ± DMARDs	Golimumab50 ± DMARDs	Golimumab100 ± DMARDs
Baseline HAQ (mean)		**1.05**	**0.96**	**1.04**
W24 HAQ (mean)		**1.07**	**0.63**	**0.65**
Δ from baseline at W24 (mean)		**-0.03**	**0.33**	**0.39**
Centocor's analysis[1]	**Randomized Patients**	**113**	**146**	**146**
	Proportion with Δ change from baseline at W24 ≥ 0.3	**23%**	**43%**	**52%**
	95 % CI	**15-31%**	**35-51%**	**44-60%**
	p-value	**—**	**< 0.001**	**< 0.001**
Sensitivity Analysis using observed data (Dr. Buenconsejo's analysis)	**N**	**104**	**139**	**143**
	Proportion with Δ change from baseline at W24 ≥ 0.3	**22%**	**43%**	**52%**
	p-value	**—**	**0.0006**	**<0.0001**

HAQ score is from 0 (best score) to 3 (worst score).

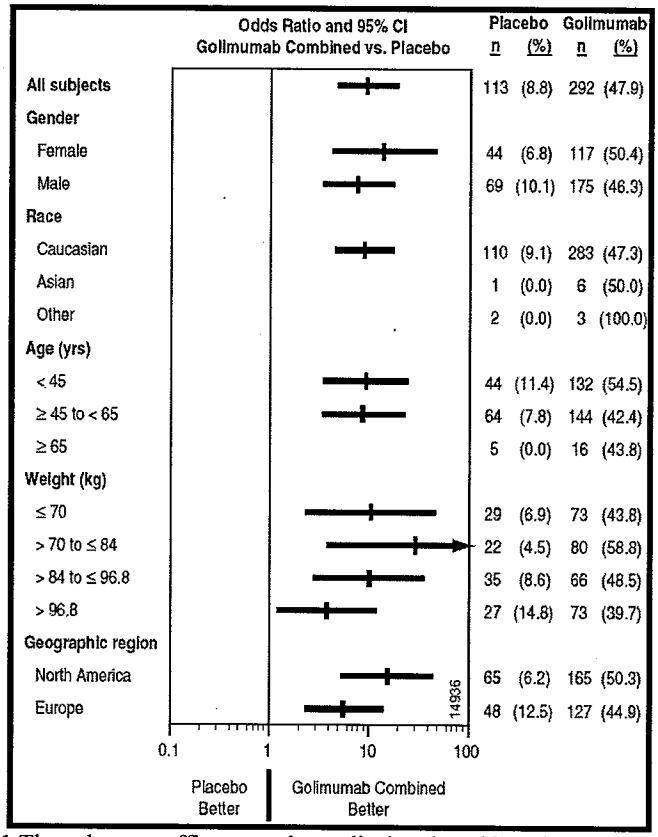
1 For Centocor's analysis, treatment failure rules were not applied. For patients in the placebo and golimumab50 groups who met early escape criteria at Week 16, the non-missing HAQ score was replaced with the Week 16 HAQ score. There was no missing data imputation. This was not an ITT analysis.

Reference: Adapted from the Final Study Report for Study 8, Table 25, Page 131 and VISRA dataset for Study 8.

6.2.6 Subpopulations – PsA

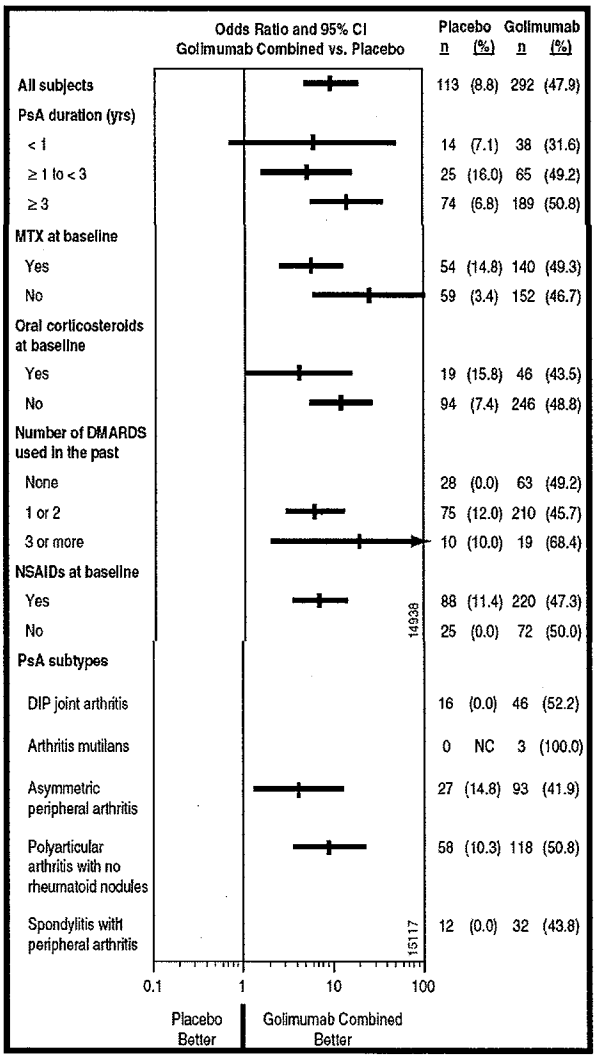
Figure 6.22 presents the subgroup efficacy analyses of the combined golimumab groups compared to the placebo group, using the primary efficacy endpoint, by demographics. Figure 6.23 presents the subgroup efficacy analyses of the combined golimumab groups compared to the placebo group, using the primary efficacy endpoint, by disease duration, RF status, and baseline medication use. In these subgroup analyses, the combined golimumab groups were used instead of the individual low and high dose groups to increase the sample size and because there was no evidence of a dose response between the low and high dose groups. Treatment with golimumab appeared to exert a positive effect for all subgroups analyzed.

Figure 6.22: Efficacy (i.e., ACR 20 responders at Week 14) of the combined golimumab groups vs. the placebo group by demographic subgroups in Study 8[1]



1 The subgroup efficacy analyses display the odds ratios and the 95% confidence intervals of the odds ratios. The odds ratio is g/(1-g) divided by p/(1-p). Where g is the proportion of patients in the golimumab combined groups with an ACR 20 response at W14 and p is the proportion of patients in the placebo group with an ACR 20 response at W14. The vertical bars in the figure represent the odds ratio and the horizontal bars represent the 95% confidence intervals (CIs) of the odds ratio. The x axis is on a logarithmic scale. The ACR 20 response at Week 14 was the primary efficacy analysis for Study 8.
Reference: Adapted from the final study report for Study 8, Attachment 3.70, Page 481

Figure 6.23: Efficacy (i.e., ACR 20 responders at Week 14) of the combined golimumab groups vs. the placebo group by PsA duration, baseline medications, and PsA subtypes in Study 8[1]



1 The subgroup efficacy analyses display the odds ratios and the 95% confidence intervals of the odds ratios. The odds ratio is g/(1-g) divided by p/(1-p). Where g is the proportion of patients in the golimumab combined groups with an ACR 20 response at W14 and p is the proportion of patients in the placebo group with an ACR 20 response at W14. The vertical bars in the figure represent the odds ratio and the horizontal bars represent the 95% confidence intervals (CIs) of the odds ratio. The x axis is on a logarithmic scale. The ACR 20 response at W14 was the primary efficacy analysis for Study 8.

Reference: Adapted from the final study report for Study 8, Attachment 3.71, Page 482; Attachment 3.72, Page 483; Attachment 3.73, Page 484

Distinct from what was observed in the RA trials, concomitant MTX did not appear to improve responses in PsA patients treated with golimumab. As summarized in Table 6.24, treatment with golimumab resulted in a greater proportion of ACR 20 responders at Week 14, compared to treatment with placebo. However, concomitant MTX usage did not appear to affect the proportion of ACR responders in the golimumab groups. Based on these results, it would appear to be reasonable to allow golimumab to be administered irrespective of MTX use for PsA patients.

Table 6.24: Efficacy (i.e., ACR 20 responders at Week 14) by MTX subgroup analysis in Study 8[1]

	Placebo + MTX	Golimumab50 + MTX	Golimumab100 + MTX
Patients who received MTX at baseline, n	55	71	71
ACR 20 responders at Week 14	**15%**	**54%**	**45%**
	Placebo	**Golimumab50**	**Golimumab100**
Patients who did not receive MTX at baseline, n	58	75	75
ACR 20 responders at Week 14	**3%**	**48%**	**45%**

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. ACR 20 responders at Week 14 were the first co-primary efficacy endpoint in Study 8.
Reference: Adapted from Final Study Report for Study 8; Table 18, Page 116.

6.2.7 Analysis of Clinical Information Relevant to Dosing Recommendations – PsA

Centocor studied two different SC golimumab treatment regimens in their one Phase 3 PsA trial [golimumab 100 mg given once every 4 weeks (golimumab100) and golimumab 50 mg given once every 4 weeks (golimumab50)]. All patients may have received stable doses of MTX, corticosteroids (equivalent to ≤ 10 mg prednisone/day), and/or NSAIDs during the study.

Centocor requests that 50 mg of SC golimumab be used once monthly with or without MTX. See section 6.2.6 (Subpopulations – PsA) for a discussion of the concomitant use of MTX. Centocor does not propose the use of the higher golimumab dose in PsA and Centocor does not propose dose regimen modification or titration for individual patient subgroups.

There was no evidence of clear dose response. The golimumab50 group had similar responses as the golimumab100 group (see Section 6.2.4 Analysis of Sign and Symptom Endpoints – PsA). This medical officer agrees with Centocor's proposal that only the lower dose (golimumab50) be used with or without MTX for the treatment of PsA.

6.2.8 Persistence of Efficacy, Tolerance, and Efficacy by Immunogenicity – PsA

As shown in Table 6.25, golimumab treatment resulted in a similar or increased proportion of ACR 20, 50, and 70 responders at Week 24 compared to Week 14. There was no evidence of drug tolerance. See Section 6.2.4 Analysis of Sign and Symptom Endpoints – PsA for more details.

Similar to RA, immunogenicity to golimumab was low in Study 8, occurring in only 13 of 366 (4%) PsA patients tested. The very low number of HAHA positive patients makes interpretation of ACR

responses in the HAHA positive subgroup difficult. However, in general, responses were similar to responses seen in the HAHA negative/undetectable group (ACR 20 response was 39% for HAHA positive patients vs. 49% for HAHA negative/undetectable patients) such that immunogenicity does not appear to exert a large effect on ACR responses. There was no difference in the proportion of ACR50 responders in HAHA positive vs. HAHA negative/undetectable subgroups (31% vs. 30%).

Table 6.25: Patients with ACR 20 or ACR 50 response at Week 24 for patients with positive HAHA who received golimumab in Study 8

	Golimumab50 ± MTX	Golimumab100 ± MTX	Placebo to Golimumab50 ± MTX	Golimumab50 to Golimumab100± MTX	All Golimumab Groups
Treated patients who received golimumab	146	146	51	28	343
Treated patients who received golimumab with appropriate samples	114	143	51	28	336
Patients who received golimumab with HAHA at anytime, n (%)	5 (4%)	7 (5%)	0 (0%)	1 (4%)	13 (4%)
ACR 20 responders, n (%)	2 (40%)	3 (43%)	N/A	0 (0%)	5 (39%)
ACR 50 responders, n (%)	1 (20%)	3 (43%)	N/A	0 (0%)	4 (31%)

Reference: Final Study Report for Study 8, Table 28, Pages 144-145

6.2.9 Additional Efficacy Issues/Analyses – PsA

There have been no comparative trials of the efficacy of golimumab to another TNF inhibitor in the treatment of the signs of symptoms of PsA, however given that 3 other TNF inhibitors have been approved for PsA, it is of interest to know whether golimumab may have similar effects. The limitations of cross-study comparisons have been previously discussed [see Section 6.1.9 (Additional Efficacy Issues/Analyses – RA)], so the results of the following analysis are not definitive. Nonetheless, as shown in Table 6.26, the four TNF inhibitors had large absolute treatment effects in the proportion of patients with ACR 20 response, ranging from 37% to 47% and golimumab appeared to have similar efficacy in the treatment of signs and symptoms of PsA.

Table 6.26: ACR 20 responders in patients with active PsA in TNF inhibitor trials[1]

Golimumab trial in patients with active PsA			
	Placebo ± MTX (n=113)	**Golimumab50 ± MTX (n=146)**	**Golimumab100 ± MTX (n=146)**
ACR 20 responders at Week 14	**9%**	**51%**	**45%**
Infliximab trial in patients with active PsA			
	Placebo ± MTX (n=100)	**Infliximab 5 mg/kg every 8 week[2] ± MTX (n=100)**	
ACR 20 responders at Week 14	**11%**	**58%**	
Etanercept trial in patients with active PsA			
	Placebo ± MTX (n=104)	**Etanercept 25 mg twice weekly ± MTX (n=101)**	
ACR 20 responders at Month 6	**13%**	**50%**	
Adalimumab trial in patients with active PsA			
	Placebo ± MTX (n=162)	**Adalimumb 40 mg every other week ± MTX (n=151)**	
ACR 20 responders at Week 12	**14%**	**58%**	

1 Results obtained from the product labels.
2 Infliximab dosed initially at Weeks 0, 2, and 6.

6.3 Indication – Treatment of [redacted] Ankylosing Spondylitis (AS) b(4)

Centocor proposes the following AS indication: "SIMPONI is indicated for [redacted] adult patients with active disease."

6.3.1 Methods – AS

Study 9 served as the critical trial for the evaluation of the efficacy of SC golimumab in the treatment of signs and symptoms of AS. This trial was well-controlled and had acceptable endpoints. As with PsA, one trial in AS was considered sufficient to support the efficacy of SC golimumab in the treatment of AS if the efficacy of SC golimumab was demonstrated in RA. Since there was one trial in AS, the entire efficacy results are evaluated in this section.

6.3.2 Demographics and Baseline Characteristics - AS

Table 6.27 displays the baseline demographics in the AS trial (i.e., Study 9). The three treatment groups in Study 9 had similar baseline demographics. The patients in Study 9 were typical of an AS population — mostly young males. The racial demographics are consistent with the regional enrollment (e.g., 24% of the patients were Asian and 23% of the total study population was from Asia).

Table 6.27: Baseline demographics in the AS trial (i.e., Study 9)[1]

		Placebo ± DMARDs[1] (n=78)	Golimumab50 ± DMARDs[1] (n=138)	Golimumab100± DMARDs[1] (n=140)
Age	Mean (SD)	41 (13) years	39 (12) years	39 (11) years
Sex	Female	30%	26%	30%
	Male	71%	74%	70%
Race	Caucasian	73%	75%	73%
	Asian	23%	23%	25%
	Black	1%	0%	1%
	Other	3%	2%	1%
Weight	Mean (SD)	78 (18) kg	75 (18) kg	80 (19) kg
Height	Mean (SD)	171 (10) cm	171 (9) cm	171 (10) cm
Region[1]	Europe & Canada	56%	53%	51%
	Asia	22%	22%	25%
	United States	22%	25%	24%

1 European countries included Belgium, Finland, France, Germany, the Netherlands and Asian countries included Korea and Taiwan

Reference: Adapted from the Final Study Report for Study 9, Table 9, Pages 77-78; also adapted from Demographics Dataset for Study 9

Table 6.28 displays the baseline disease characteristics in the AS trial (i.e., Study 9). The patients in the three treatment groups had similar baseline disease activity, durations of morning stiffness, HLA-B-27 positivity, and prior joint procedures. Patients in the placebo group had a slightly increased duration of AS and duration of inflammatory back pain compared to the golimumab groups.

Table 6.28: Baseline disease characteristics in the AS trial (i.e., Study 9)

		Placebo ± DMARDs[1] (n=78)	Golimumab50 ± DMARDs[1] (n=138)	Golimumab100± DMARDs[1] (n=140)
Duration of AS, mean (SD)		10.8 (10) years	7.9 (8) years	8.0 (8) years
Duration of inflammatory back pain, mean (SD)		16.1 (11) years	13.6 (10) years	13.2 (10) years
Duration of morning stiffness, mean (SD)		1.3 (0.5) hours	1.3 (0.5) hours	1.4 (0.5) hours
HLA-B27 positive		85%	82%	84%
Prior joint procedure		26%	25%	23%
Prior extra-spinal features	Uveitis	32%	20%	21%
	Enthesitis	31%	36%	41%
	Peripheral arthritis	36%	36%	31%
CRP mg/dL, median		1.2	1.1	0.9
Patient's total back pain, median (0-10)		8	8	8
Morning stiffness, median (0-10)		7	7	8
Global disease activity (patient), median (0-10)		7	7	7
Clinical Indices (median)	BASDAI (0-10)	6.6	6.5	7.0
	BASFI (0-10)	4.9	5.0	5.4
	BASMI (0-10)	4.0	3.0	3.0

Reference: Adapted from the Final Study Report for Study 9, Table 10, Pages 79-80, Table 11, Pages 81-82, Table 12, Pages 83-84; Table 1.10, Pages 209

Table 6.29 displays the proportion of patients who received TNF inhibitors, other DMARDs, immunosuppressive products, corticosteroids, and/or NSAIDs prior to enrollment in the AS trial (i.e.,

Study 9). 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 9.

There were no significant differences in the proportions of patients in the three treatment groups who received TNF inhibitors, other DMARDs, immunosuppressives, corticosteroids, and/or NSAIDs in the past. Only 1 (1%) patient in the golimumab100 group received a TNF inhibitor in the past (i.e., patients were excluded from participation if they received a TNF inhibitor in the past). In Study 9, 55%, 44%, 30%, 5%, 1%, 42%, and 99% of patients in Study 9 received a DMARD, sulfasalazine, MTX, hydroxychloroquine, an immunosuppressive product, steroid, and an NSAID in the past, respectively.

Table 6.29: Percent of patients who received TNF inhibitors, other DMARDs, immunosuppressives, corticosteroids, and/or NSAIDs prior to enrollment in Study 9[1]

	Placebo ± DMARDs[1] (n=78)	Golimumab50 ± DMARDs[1] (n=138)	Golimumab100 ± DMARDs[1] (n=140)
Received a TNF inhibitor[2]	**0%**	**0%**	**1%**
Received ≥ 1 DMARD	**56%**	**54%**	**56%**
Sulfasalazine	46%	43%	44%
MTX	28%	31%	31%
Hydroxychloroquine	5%	6%	4%
Gold preparations	4%	3%	3%
Leflunomide	1%	3%	1%
Received ≥ 1 immunosuppressive	**1%**	**1%**	**2%**
Cyclosporine	1%	1%	1%
Received systemic corticosteroids	**40%**	**47%**	**39%**
Received NSAIDs	**100%**	**99%**	**99%**

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 population
2 Patients who received any dose of a biologic TNF inhibitor in the past were excluded from enrollment in Study 9. One patient in the golimumab100 group received infliximab prior to enrollment.
Reference: Adapted from Final Study Report for Study 9, Table 1.17, Page 223

Table 6.30 displays the use of MTX, sulfasalazine, hydroxychloroquine, steroids, and/or NSAIDs at baseline in Study 9. 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, sulfasalazine, hydroxychloroquine, steroids, and/or NSAIDs at baseline. In Study 9, 20%, 26%, 1%, 16%, and 90% of the patients received MTX, sulfasalazine, hydroxychloroquine, steroids, and NSAIDs at baseline, respectively.

For the three treatment groups, the proportions of patients who received oral steroids and NSAIDs were similar at baseline, at Week 14, and at Week 24 during Study 9 (see Table 6.31).

Table 6.30: Patients who received MTX, SSZ, HCQ, corticosteroids, or NSAIDs at baseline in Study 9[1]

	Placebo ± DMARDs[1] (n=78)	Golimumab50 ± DMARDs[1] (n=138)	Golimumab100 ± DMARDs[1] (n=140)
Received MTX at baseline	19%	21%	20%
For patients who received MTX, mean (SD) weekly dose	14 (5) mg	14 (4) mg	13 (3) mg
Received SSZ at baseline	31%	24%	26%
For patients who received SSZ, mean (SD) daily dose	1.8 (0.6) g	1.6 (0.6) g	1.7 (0.6) g
Received HCQ at baseline	3%	1%	1%
For patients who received HCQ, mean (SD) daily dose	250 (71) mg	300 (141) mg	400 (N/A) mg
Received oral steroids at baseline	17%	19%	13%
For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	7 (3) mg	7 (3) mg	5 (3) mg
Received NSAIDs at baseline	92%	90%	88%

1 Randomized patients
2 Patients may have taken stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, 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
Reference: Adapted from Final Study Report for Study 9, Table 13, Page 86.

Table 6.31 displays the proportion of patients who received MTX, SSZ, and HCQ at baseline and during the 24 week controlled period. A similar proportion of patients in the treatment groups received MTX, SSZ, and HCQ at baseline and during the trial.

About 14%, 14%, and 13% of the patients in the placebo, golimumab50, and golimumab100 groups received ≥ 2 or more DMARDS (not counting golimumab) during the 24 week period. For the patients who received ≥ 2 or more DMARDS, 93% of the time patients received concomitant MTX and SSZ. One patient in Study 9 received all 3 DMARDS, MTX, SSZ, and HCQ (not counting golimumab).

Table 6.31: Proportion of patients who received MTX, SSZ, and HCQ at baseline and during the 24 week controlled period in Study 9[1]

	Placebo ± DMARDs[1] (n=78)	Golimumab50 ± DMARDs[1] (n=138)	Golimumab100 ± DMARDs[1] (n=140)
Received MTX at baseline	19%	21%	20%
Received MTX during 24 week controlled period	19%	25%	19%
Received SSZ at baseline	31%	24%	26%
Received SSZ during 24 week controlled period	32%	28%	29%
Received HCQ at baseline	3%	1%	1%
Received SSZ during 24 week controlled period	5%	2%	1%

1 Randomized patients
2 Patients may have taken stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, 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
Reference: Adapted from Final Study Report for Study 9, Table 13, Page 86.

6.3.3 Patient Disposition - AS

Table 6.32 displays the patient disposition through Week 24 in the AS trial (i.e., Study 9). A lower proportion of patients in the golimumab groups, compared to the placebo group, entered early escape. There was no evidence of a dose response.

A slightly greater proportion of patients in the golimumab groups, compared to the placebo group, had an adverse event leading to discontinuation (DAE). For a discussion of the DAEs in Study 9 see Table 7.6.4 (Drug-Disease Interactions).

Table 6.32: Patient disposition through Week 24 in the AS trial (i.e., Study 9)

	placebo ± DMARDs	golimumab50 ± DMARDs	golimumab100 ± DMARDs
Randomized[1], n	78	138	140
Received ≥ 1 dose of SC agent[2], n	78	137	140
Entered the escape phase at Week 16[3]	53%	18%	24%
Discontinued SC study agent	3%	4%	2%
Adverse event	1%	3%	2%
Other	0%	0%	0%
Lost to follow-up	0%	1%	0%
Unsatisfactory therapeutic effect	1%	0%	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. Any patient who had < 20% improvement from baseline in both total back pain and morning stiffness at Week 16 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; Final Study Report for Study 9, Table 4, Page 66; Table 5, Page 68; Disposition Datasets for Studies 8 and 9

6.3.4 Analysis of Sign and Symptom Endpoints – AS

The primary efficacy endpoint in the AS trial (Study 9) was the proportion of patients with an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. A patient was classified as having achieved an ASAS 20 response at Week 14 if both of the following was achieved at Week 14:

1. A relative improvement of ≥ 20% from baseline and an absolute improvement from baseline of ≥ 1 on 0 to 10 cm scales in ≥ 3 of the following 4 domains:

   - Patient global
   - Total back pain, using the average total back pain over the past week
   - Function using the Bath AS Functional Index (BASFI)
   - Mean of the last two stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI).

2. Absence of deterioration from baseline (deterioration defined as ≥ 20% worsening and absolute worsening of ≥ 1 on a 0 to 10 cm scale) in the potential remaining domain.

A patient was defined as having an ASAS 5/6 response if they achieved a 20% improvement from baseline in 5 of the following 6 domains: total back pain (0 to 10), patient global (0 to 10), function (BASFI score from 0 to 10), the mean morning stiffness score in the BASDAI (0 to 10), CRP, and spine mobility (lumbar side flexion). See Table 6.33 for the definitions of BASFI, BASDAI, and BASMI.

Table 6.33: The Bath AS Function Index (BASFI), Bath AS Disease Activity Index (BASDAI), and the Bath AS Metrology Index (BASMI)

Instrument	Definition	Range
Bath AS Functional Index (BASFI)	**A functional instrument (a higher score indicates worse function), was calculated as the mean of 10 scales (8 and 2 scales are related to the functional capacity of a patient and the patient's ability to cope with everyday life, respectively).**	**0 to 10**
Bath AS Disease Activity Index (BASDAI)	**A summary of 6 self-assessments (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness). The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1. The mean of the last two scales provide an assessment of stiffness that is used in the ASAS.**	**0 to 10**
Bath AS Metrology Index (BASMI)	**Comprises of the sum of 5 measures of hip and spine mobility [i.e., tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe).**	**0 to 10**

Table 6.34 displays the proportion of ASAS 20, ASAS 40, and ASAS 5/6 responders at Weeks 14 and 24 in the AS trial (i.e., Study 9). Both the low and high dose golimumab treatment groups had greater proportions of ASAS 20 responders at Week 14 compared to the placebo group. These results were statistically significant and the absolute treatment effect sizes between the golimumab groups and the placebo group were 37% to 38%. These absolute treatment effect sizes were maintained at Week 24.

The low and high dose golimumab groups had greater proportions of ASAS 40 and ASAS 5/6 responders than the placebo group at Week 14. 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.

Table 6.34: Major signs and symptom results in the AS trial (i.e., Study 9)

		Placebo ± DMARDs[1] (n=78)	Golimumab50 ± DMARDs[1] (n=138)	Golimumab100 ± DMARDs[1] (n=140)	Combined Golimumab ± DMARDs[1] (n=278)
ASAS 20 responders	Week 14[2]	22%	59%	60%	60%
	p-value vs. placebo	—	< 0.001	< 0.001	< 0.001
	Week 24[3]	23%	56%	66%	61%
ASAS 40 responders	Week 14	15%	45%	49%	47%
	Week 24	15%	44%	54%	49%
ASAS 5/6 responders[4]	Week 14	8%	50%	49%	49%
	Week 24	13%	49%	51%	50%

1 Patients may have been taking stable doses of concomitant MTX, HCQ, SSZ, 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.
2 The primary efficacy endpoint in Study 9 was the proportion of patients with an ASAS 20 response at Week 14.
3 The proportion of patients with an ASAS 20 response at Week 24 was 1 of 3 pre-specified secondary endpoints without multiplicity adjustments.
4 ASAS 5/6 responders achieved a 20% improvement from baseline in 5 of the following 6 domains: total back pain (VAS 0 to 10 cm), patient global (VAS 0 to 10 cm), function (BASFI score), the mean morning stiffness score in the BASDAI (VAS 0 to 10 cm), CRP, and spine mobility (lumbar side flexion).
Reference: Adapted from Final Study Report for Study 9, Table 16, Page 104; Table 18, Page 107; Table 23, Page 111; Table 3.11, Page 361.

Table 6.35 displays the proportion of patients with a Bath AS Disease Activity Index (BASDAI) response at Weeks 14 and 24 in the AS trial (i.e., Study 9). A greater proportion of patients in the low and high dose golimumab groups, compared to the placebo group, had BASDAI 20, 50, and 70 responses at Week 14. The treatment effects were maintained at Week 24. There was no evidence of a dose response between the low and high dose golimumab groups.

Table 6.35: Bath AS Disease Activity Index (BASDAI)[1] responders in the AS trial (i.e., Study 9)[2]

		placebo ± DMARDs	golimumab50 ± DMARDs	golimumab100 ± DMARDs
Patients in Week 14 analyses		78	133	137
Patients in Week 24 analyses		75	130	138
BASDAI 20 responders	Week 14[3]	36%	72%	67%
	Week 24[4]	28%	70%	67%
BASDAI 50 responders	Week 14[3]	15%	46%	41%
	Week 24[4]	15%	51%	48%
BASDAI 70 responders	Week 14[3]	5%	29%	24%
	Week 24[4]	8%	30%	35%

1 The Bath AS Disease Activity Index (BASDAI) contains 6 patient-reported outcomes (i.e., fatigue, spinal pain, joint pain, enthesitis, overall level of morning stiffness, and duration of morning stiffness), each on a 0-10 scale. The first 4 scales are weighted by 0.2 and the last two are weighted by 0.1 to produce a BASDAI range of 0-10. Week 14 BASDAI 20 responders are the proportion of patients that have at least a 20% improvement in the 0-10 BASDAI score from baseline at Week 14. Similarly, Week 24 BASDAI 20 responders are the proportion of patients that have at least a 20% improvement in the 0-10 BASDAI score from baseline at Week 24. The BASDAI responders were some of the 105 pre-specified other sign and symptom endpoints in Study 9.

2 Patients may have been taking stable doses of concomitant MTX, HCQ, SSZ, 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.

3 For the Week 14 BASDAI responders, no treatment failure rules were applied and only observed data was used.

4 For the Week 24 BASDAI responders, no treatment failure rules were applied and only observed data was used. For patients who entered early escape at Week 16 in the placebo or golimumab50 groups, missing data at Week 24 was replaced with the corresponding value at Week 16.

Reference: Adapted from Final Study Report for Study 9, Table 24, Page 113; Table 3.12, Page 362; Table 3.13, Page 363

Table 6.36 displays the median change from baseline at Week 14 in the 4 components of the ASAS in the AS trial (i.e., Study 9). Treatment with golimumab showed greater improvement in all 4 components of the ASAS at Week 14. There was no evidence of a dose response between the low and high dose golimumab groups.

Table 6.36: Median change from baseline at Week 14 in the 4 components of the ASAS in Study 9

	Placebo ± MTX	Golimumab50 ± MTX	Golimumab100 ± MTX
Patient Global Assessment of Disease Activity, (0-10)	**-0.8 (n=78)**	**-2.8 (n=132)**	**-3.4 (n=137)**
Total Back Pain, (0-10)	**-0.8 (n=78)**	**-3.5 (n=132)**	**-3.6 (n=137)**
Function (using the BASFI) (0-10)	**0.1 (n=78)**	**-1.4 (n=138)**	**-1.5 (n=140)**
Stiffness (last two patient-reported outcomes in the BASDAI), (0-10)	**-0.5 (n=78)**	**-3.2 (n=133)**	**-3.3 (n=137)**

1 These endpoints were included in the 105 other pre-specified endpoints related to signs and symptoms (no multiplicity adjustments). Patients may have been taking stable doses of concomitant MTX, HCQ, SSZ, 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 9, Table 25, Page 114; Table 3.17, Page 368; Table 19, Page 107; Table 3.20, Page 372; also adapted from the VISRA JMP dataset for Study 9.

6.3.5 Analysis of Functional and Mobility Endpoints – AS

Table 6.37 displays the median change in the Bath AS functional and mobility indexes (i.e., BASFI and BASMI) at Weeks 14 and 24 in Study 9. See Table 6.33 in Section 6.3.4 for the definitions of the BASFI and BASMI instruments. Patients in the low and high dose golimumab groups, compared to the placebo group, had greater improvements in the BASFI at Weeks 14 and 24. There was no evidence of dose response.

There was no difference in the change from baseline in the Week 14 and Week 24 BASMI in the low and high dose golimumab groups compared to the placebo group. This finding is not inconsistent with the primary efficacy findings in that reduction in hip and spine mobility in AS occur as a result of long durations of disease and treatment effects may not have been possible to demonstrate in the timeframe of this clinical trial.

Table 6.37: Median change in the Bath AS functional and mobility indexes (i.e., BASFI and BASMI) at Weeks 14 and 24 in Study 9

		placebo ± DMARDs (n=78)[1]	golimumab50 ± DMARDs (n=138)[1]	golimumab100 ± DMARDs (n=140)[1]
BASFI[2]	Baseline (0-10)	4.9	5.0	5.4
	Week 14	5.0	3.6	3.5
	Δ from baseline at Week 14[4]	0.1	-1.4	-1.5
	Patients with W24 BASFI values	73	130	138
	Δ from baseline at Week 24[5]	0.4	-1.6	-1.6
BASMI[3]	Baseline (0-10)	4	3	3
	Week 14	4	3	3
	Δ from baseline at Week 14[4]	0	0	0
	Patients with W24 BASMI values	74	129	138
	Δ from baseline at Week 24[5]	0	0	-0.2

Patients may have taken stable doses of concomitant MTX, HCQ, SSZ, 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

2 The BASFI (Bath AS Functional Index) was a functional instrument from 0-10 that includes 10 scales that measure the functional capacity of a patient and the patient's ability to cope with everyday life. Centocor proposes to place BASFI data in the Clinical Studies section of the label.

3 BASMI (Bath AS Metrology Index) comprises of the sum of 5 measures of hip and spine mobility [i.e., tragus-to-wall, lumbar flexion (Schober test), cervical rotation, lumbar side flexion, and intermalleolar distance] that are each categorized as 0 (mild), 1 (moderate), or 2 (severe). The BASMI ranges from 0-10. Centocor does not propose to place BASMI data in the Clinical Studies section of the label.

4 The change from baseline in the BASFI at Week 14 and the change from baseline in the BASMI at Week 14 were 2 of the 3 pre-specified secondary endpoints without multiplicity adjustments. For the Week 14 BASFI, patients who had treatment failures had a change from baseline set to 0. If there were no data from baseline through Week 14, then the change from baseline was imputed by the median change from baseline based on all patients' data from the same stratum (screening CRP). If the Week 14 value was missing, a LOCF procedure was used to impute BASFI.

5 The change from baseline in the BASFI at Week 24 and the change from baseline in the BASMI at Week 24 were 2 of 105 other sign and symptom endpoints in Study 9. For the Week 24 BASFI and BASMI data, no treatment failures applied; if patients in the placebo or golimumab50 groups met early escape at Week 16, the non-missing values at Week 24 were replaced with the Week 16 value; and only observed data were used.

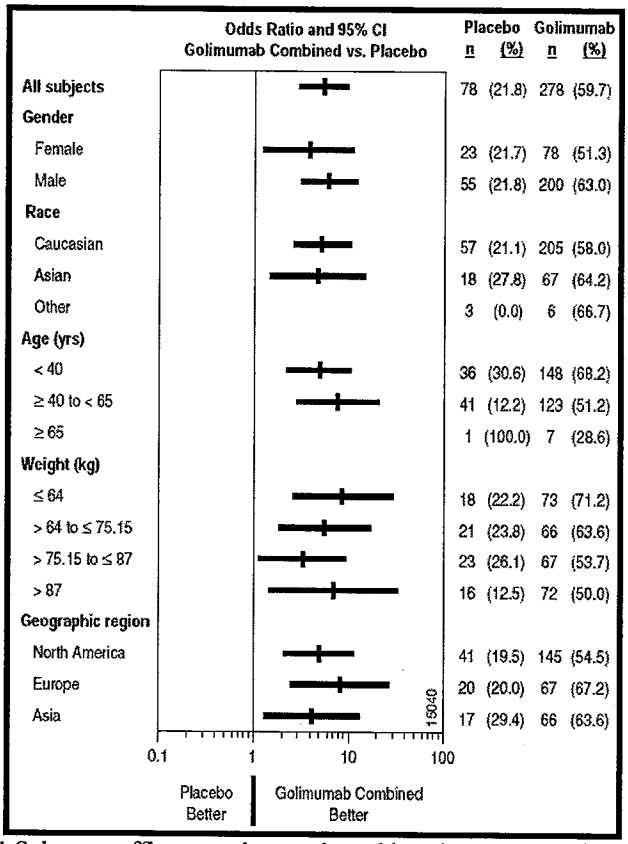
Reference: Adapted from Final Study Report for Study 9, Table 19, Page 107; Table 3.18, Page 370; Table 20, Page 108; Table 26, Page 117; Table 12, Page 83-84; also adapted from the BASFI JMP datasets in Study 9.

6.3.6 Subpopulations – AS

Figure 6.38 displays subgroup efficacy analyses, using the primary efficacy endpoint (ASAS responders at Week 14), by demographic subgroups in Study 9. The combined golimumab group was used in these analyses to increase the sample size and because there was no dose response between the low and high dose groups. Figure 6.39 displays subgroup efficacy analyses, using the primary efficacy endpoint (ASAS responders at Week 14), by disease duration, HLA-B27 status, and baseline concomitant medication use in Study 9. There was no clear evidence of a differential response

between the combined golimumab groups compared to the placebo group in the proportion of ASAS 20 responders at Week 14 in the demographic, disease duration, baseline medication use, and HLA-B27 status subgroups.

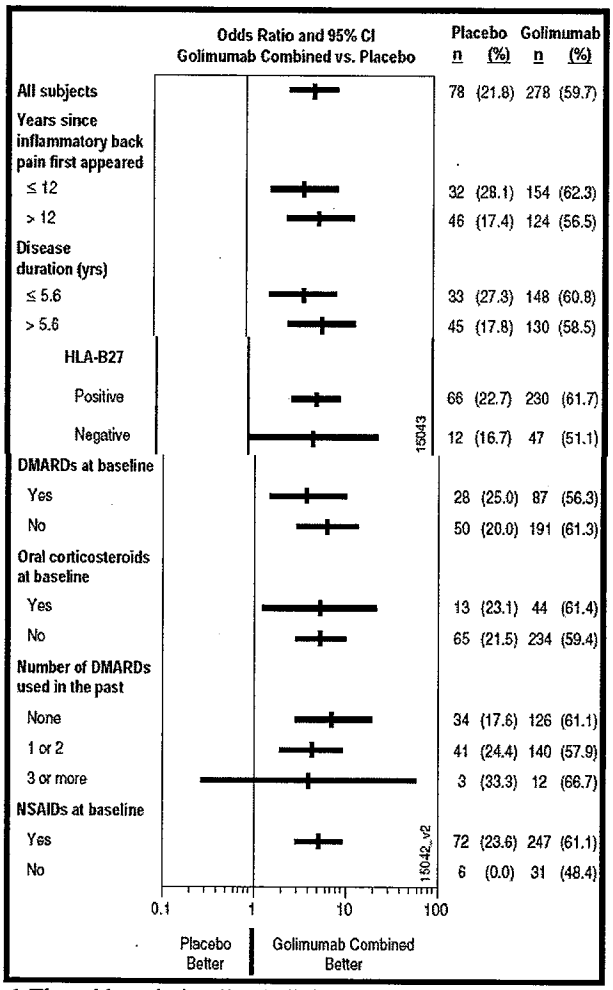
Figure 6.38: Efficacy (i.e., ASAS 20 responders at Week 14) of the combined golimumab groups vs. the placebo group by demographic subgroups in Study 9[1]



1 Subgroup efficacy analyses using odds ratios and 95% confidence intervals of the odds ratios. The odds ratio is g/(1-g) divided by p/(1-p). Where g is the proportion of patients in the golimumab combined groups with an ASAS 20 response at W14 and p is the proportion of patients in the placebo group with an ASAS 20 response at W14. The vertical bars in the figure represent the odds ratio and the horizontal bars represent the 95% confidence intervals of the odds ratio. The x axis is on a logarithmic scale. The ASAS 20 response at W14 was the primary efficacy analysis for Study 9, using the randomized population.

Reference: Adapted from the final study report for Study 9, Attachment 3.58, Page 419

Figure 6.39: Efficacy (i.e., ASAS 20 responders at Week 14) of the combined golimumab groups vs. the placebo group by disease duration, HLA-B27 status, and baseline concomitant medication use in Study 9[1]



1 The odds ratio is g/(1-g) divided by p/(1-p). Where g is the proportion of patients in the golimumab combined groups with an ASAS 20 response at W14 and p is the proportion of patients in the placebo group with an ASAS 20 response at W14. The vertical bars in the figure represent the odds ratio and the horizontal bars represent the 95% confidence intervals (CIs) of the odds ratio. The x axis is on a logarithmic scale. The ASAS 20 response at W14 was the primary efficacy analysis for Study 9, using the randomized population.

Reference: Adapted from the final study report for Study 9, Attachment 3.59, Page 420; Attachment 3.60, Page 421; Attachment 3.61, Page 422.

6.3.7 Analysis of Clinical Information Relevant to Dosing Recommendations – AS

Centocor studied two different SC golimumab treatment regimens in their one Phase 3 AS trial [golimumab 100 mg given once every 4 weeks (golimumab100) and golimumab 50 mg given once

every 4 weeks (golimumab50)]. All patients may have received stable doses of MTX, sulfasalazine hydroxychloroquine, corticosteroids (equivalent to ≤ 10 mg prednisone/day), and/or NSAIDs during the study. Few patients received hydroxychloroquine (1-3%), MTX (19-21%), oral steroids (13-19%), or sulfasalazine (24-31%) at baseline and during the trial and there was significant exposure to NSAIDs (88-92%) at baseline and during the trial.

Centocor requests that 50 mg of SC golimumab be used once monthly. Centocor does not propose the use of the higher golimumab dose in AS and Centocor does not propose dose regimen modification or titration for individual patient subgroups.

There was no evidence of clear dose response. The golimumab50 group had similar responses as the golimumab100 group (see Section 6.3.4 Analysis of Sign and Symptom Endpoints – AS). This medical officer agrees with Centocor's proposal that only the lower dose (golimumab50) be used for the treatment of AS. Given that almost all patients received concomitant NSAIDs, the label should detail the concomitant NSAID use in Study 9.

6.3.8 Persistence of Efficacy, Tolerance, and Efficacy by Immunogenicity – AS

In Study 9, all of the golimumab treatment groups had similar or increased proportion of ASAS 20 and ASAS 40 responders and BASDAI 20, 50, and 70 responders at Week 24 compared to Week 14. There was no evidence of drug tolerance. See Section 6.3.4 Analysis of Sign and Symptom Endpoints – AS for more details.

See Table 6.40 for a subgroup efficacy analysis, using ASAS 20 responders at Week 24, in patients who received golimumab with appropriate samples by HAHA positive status in the one Phase 3 AS trial. There was no clear evidence that positive antibody responses to golimumab resulted in decreased efficacy because there were too few patients with HAHA to make firm conclusions. The total number of patients in Study 9 who had positive HAHA (human antibody to golimumab) was low [11 of 312 (4%) patients who received golimumab with appropriate samples had positive HAHA). The ASAS 20 response at Week 24 for patients with positive HAHA was slightly lower than for patients with negative/undetectable HAHA (46% vs. 54%). However, the number of patients with a positive HAHA was too small to make conclusions about the relationship between antibody response and efficacy.

Table 6.40: Patients with ASAS 20 response at Week 24 for golimumab-treated patients with positive HAHA in Study 9

	Golimumab50 ± DMARDs	Golimumab100 ± DMARDs	Placebo to Golimumab50 ± DMARDs	Golimumab50 to Golimumab100± ± DMARDs	All Golimumab Groups
Golimumab-treated patients	138	140	41	25	319
Golimumab-treated patients with appropriate samples	109	138	41	24	312
Golimumab-treated patients with HAHA at anytime, n (%)	5 (5%)	3 (2%)	0 (0%)	3 (13%)	11 (4%)
ASAS 20 responders, n (%)	3 (60%)	2 (67%)	N/A	0 (0%)	5 (46%)

Reference: Final Study Report for Study 9, Table 33, Page 132

6.3.9 Additional Efficacy Issues/Analyses - AS

Three other TNF inhibitors are currently approved for the treatment of the signs of symptoms of AS (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 AS.

Keeping in mind the limitations of cross-study comparisons, the analysis summarized in Table 6.41 below suggests all four TNF inhibitors had large absolute treatment effects compared to the control groups with respect to ASAS 20 responders (33% to 42%). Golimumab appeared to have similar efficacy as the other TNF inhibitors in the treatment of the signs and symptoms of AS.

Table 6.41: ASAS 20 responders in patients with active AS in TNF inhibitor trials[1]

Golimumab trial in patients with active AS			
	Placebo ± DMARDs (n=78)	**Golimumab50 ± DMARDs (n=138)**	**Golimumab100 ± DMARDs (n=140)**
ASAS 20 responders at Week 14	**22%**	**59%**	**60%**
Infliximab trial in patients with active AS			
	Placebo (n=78)	**Infliximab 5 mg/kg every 8 weeks[2] (n=201)**	
ASAS 20 responders at Week 24	**18%**	**60%**	
Etanercept trial in patients with active AS			
	Placebo ± DMARDs (n=139)	**Etanercept 25 mg twice weekly ± DMARDs (n=138)**	
ASAS 20 responders at Week 12	**27%**	**60%**	
Adalimumb trial in patients with active AS			
	Placebo (n=107)	**Adalimumab 40 mg every other week (n=208)**	
ASAS 20 responders at Week 12	**21%**	**58%**	

1 From the approved product labels
2 Infliximab dosed initially at Weeks 0, 2, and 6.

Appears This Way
On Original

7 Review of Safety

Safety Summary:

Exposure: In the entire safety database of 13 completed studies of golimumab, 2894 patients received at least one dose of golimumab (2868 and 26 patients received at least one dose of SC and IV golimumab, respectively). One dose of SC golimumab is considered to have 4 weeks of exposure given the 2-week half life of golimumab after SC administration and the dosing interval in Phase 3 trials was every 4 weeks. In the 5 Phase 3 rheumatology trials, 2210, 2057, and 1768 patients received at least 4, 24, and 52 weeks, respectively, of the proposed SC golimumab dose (50 mg) or a higher dose (100 mg) as of the last safety cut off date — patients may have been counted more than once. In the 3 RA Phase 3 trials, the 1 PsA Phase 3 trial, and the 1 AS Phase 3 trial, 1099, 355, and 314 patients, respectively, received the proposed SC golimumab dose (50 mg) or a higher dose (100 mg) for at least 52 weeks. In the 5 Phase 3 trials, the mean (SD) number of golimumab administrations for the golimumab50 and golimumab100 groups were 15 (8) and 17 (8), respectively, and the mean (SD) cumulative golimumab dose for the golimumab50 and golimumab100 groups were 743 (383) mg and 1719 (791) mg, respectively, as of the last safety cut-off date. The duration of golimumab exposure is consistent with FDA recommendations for biologic products for the treatment of rheumatologic diseases; is robust considering the recommendations for an adequate safety database described in the *2005 Premarketing Risk Assessment Guidance* and considering that golimumab could be the fifth approved TNF inhibitor; and was adequate to assess the safety of golimumab in the treatment of signs and symptoms of patients with RA, PsA, and AS.

Major Safety Results: In the controlled and uncontrolled portions of the 12 SC golimumab studies, 14 patients died (13 and 1 patients died in the rheumatologic and asthma Phase 2/Phase 3 trials, respectively). Of the 13 patients who died in the controlled and uncontrolled portions of the rheumatology Phase 2 and Phase 3 trials of SC golimumab, 1 (0.1%), 4 (0.3%), and 8 (0.6%) died in the placebo, golimumab50, and golimumab100 groups, respectively (the incidence of deaths were 0.29, 0.27, and 0.46 per 100-patient years, respectively). In the controlled portions of the 5 Phase 3 trials of RA, PsA, and AS through Week 24, 1 (0.2%), 1 (0.1%), and 2 (0.2%) of the patients in the placebo, golimumab50, and golimumab100 groups died, respectively. The exposure adjusted incidence and types of deaths (e.g., serious infections, malignancies, cardiac disorders) were consistent with those seen in other trials of biologic immunosuppressives in RA. Background rates of death in published RA cohorts are approximately 2.4 to 2.5 deaths per 100-patient years (Olmstead County RA Cohort, Gonzalez 2007), thus exposure adjusted incidence rates of death in the golimumab trials were well below rates that might be expected in this population.

In the controlled portions of the 5 Phase 3 trials, the combined golimumab group had a lower or similar proportion of SAEs, adverse events leading to discontinuation (DAEs), and AEs compared to the placebo control group. The golimumab100 group had a slightly greater proportion of SAEs and DAEs than the golimumab50 group including sepsis SAEs and DAEs.

Serious Infections: An increased risk for serious infections is a well known toxicity of TNF inhibitors, occurring at rates that approximate 5 to 6 serious infections per 100 patient-years, compared to 2-4 serious infections per 100 patient-years in RA patients taking non-biologic DMARDS (Listing 2005, Dixon 2007). In the controlled portions of the 5 Phase 3 trials, the combined golimumab group had a

similar proportion of serious infections compared to the placebo control group (2.2%, 1.5%, and 2.3% of the patients had serious infections in the placebo, golimumab50, and golimumab100 groups, respectively). In the controlled and uncontrolled portions of the rheumatology Phase 2 and Phase 3 trials, a greater proportion of patients in the combined golimumab group had serious infections compared to the placebo group [98 (4.4%) versus 17 (2.7%)]; however, the golimumab group had a lower exposure-adjusted incidence of serious infections compared to the placebo group (4.4 versus 5.7 serious infections per 100 patient-years). Golimumab rates of serious infections in these trials were lower than expected and placebo rates of serious infections in these trials were higher than expected from the published literature. There were 7 cases of tuberculosis and 4 cases of invasive fungal infections (2 cases of histoplasmosis, 1 case of coccidioidomycosis, and 1 case of pneumocystosis) in the 13 submitted golimumab studies through the last safety cut-off date. In the controlled portions of the 5 Phase 3 trials, a slightly greater proportion of patients in the golimumab groups had an infection AE and had an infection AE that required oral or parental anti-microbial therapy compared to the placebo group. Overall, the incidence and types of serious infections noted with golimumab are consistent with those seen with other TNF inhibitors.

Malignancies: In the controlled portions of the 5 Phase 3 trials, 2 (0.3%), 1 (0.1%), and 5 (0.5%) patients in the placebo, golimumab50, and golimumab100 groups developed malignancies other than NMSC and 3 (0.5%), 1 (0.1%), and 6 (0.6%) patients in the placebo, golimumab50, and golimumab100 groups developed NMSC, respectively. However, the exposure-adjusted incidence of malignancies other than NMSC was similar in the three groups (0.6, 0.7, and 0.5 malignancies other than NMSC per 100 patient-years in the placebo, golimumab50, and golimumab100 groups, respectively) and the exposure-adjusted malignancies other than NMSC rates in the golimumab and placebo groups were similar to the expected rate in the general U.S. population according to the SEER database. Of the malignancies other than NMSC, there were 3 and 0 lymphomas in the golimumab and placebo groups, respectively, and the exposure-adjusted lymphomas in the golimumab groups were slightly greater than the expected rate in the general U.S. population according to the SEER database, a finding consistent with the experience with other TNF inhibitors in rheumatic disease. The exposure-adjusted incidence of NMSC was lower in the golimumab groups compared to the placebo group (1.5, 0.6, and 0.6 NMSCs per 100 patient-years in the placebo, golimumab50, and golimumab100 groups, respectively). Of note, the rate of malignancy in the combined golimumab groups (which included a higher golimumab 200 mg dose) in a Phase 2 asthma trial was 3.5 fold higher than expected in the general U.S. population according to the SEER database . Susceptibility to malignancies in the asthma trial might be dose-related, since a higher dose of golimumab was studied or might be related to the higher doses of oral corticosteroids used (for the patients who used steroids, the mean daily oral dose of prednisone equivalents was 13 and 7 mg in the asthma and rheumatology trials, respectively).

Immunogenicity and allergic reactions: The proportion of patients who received golimumab and who developed HAHA was low. The concomitant use of golimumab and MTX was associated with a lower proportion of patients who developed HAHA. In the controlled portions of the 5 Phase 3 trials, 12 (2%) and 39 (7%) golimumab-treated patients with appropriate samples had positive HAHA in the golimumab/MTX and golimumab monotherapy groups, respectively. No golimumab-treated patient in the controlled portions of the 5 Phase 3 trials developed an anaphylactic reaction or serum sickness and there was no significant difference in the proportion of patients in the golimumab and placebo groups who developed urticaria, hypersensitivity, and/or rash. In the controlled portions of the 5

Phase 3 trials, 3.2%, 6.8%, and 9.1% of the patients in the placebo, golimumab50, and golimumab100 groups, respectively, had injection site reactions. Of the 1864 patients who received a mean of 5.4 SC golimumab injections in the controlled portions of the 5 Phase 3 trials, 1 (0.1%) patient had a severe injection-site reaction. Thus, overall, immunogenicity was uncommon with golimumab treatment, and serious allergic reactions even less so.

CHF, Demyelinating Disorders, Autoimmune Disorders, Serious Hematologic Cytopenias, and Hepatotoxicity: There was no significant difference in the exposure-adjusted rates of congestive heart failure, demyelinating disorders, autoimmune disorders, new auto-antibody formation, and serious hematological cytopenias in the golimumab-treated and placebo-treated patients. There were no "true" Hy's law cases (not confounded by baseline liver disease or concomitant hepatotoxic products) and a similar proportion of patients in the golimumab and placebo groups had post-baseline ALT elevations with similar degree of elevations.

Safety Subgroup Analyses: The safety of SC golimumab was similar in the RA, PsA, and PsA trials.

Safety of the To-Be-Marketed Presentation of SC Golimumab (PFS): Centocor proposes to market two pre-filled syringe (PFS) presentations of SC golimumab [redacted] ; and b(4) an auto-injector); however, only the liquid in a vial (LIV) presentation was used in the 24-week controlled portions of the 5 Phase 3 trials. The PFS presentation had increased subvisible particles compared to LIV in chemical comparability studies. However, the marketing of the PFS presentation is supported by the following:

1. Extrapolation of the safety and efficacy data of the LIV presentation in the RA, PsA, and AS populations.
2. No differences in the immunogenicity (proportion of patients with HAHA) after multiple-dose administration of the LIV and PFS presentations in the long-term extensions of the Phase 3 trials. Patients who switched from LIV to PFS had similar proportions of HAHA compared to patients who remained on LIV.
3. No differences in important allergic-type reactions after multiple-dose administration of the LIV and PFS presentations. No anaphylatic, serum sickness reactions, serious injection site reactions, or severe injection site reactions were seen after multiple-dose administration of the PFS presentation.
4. No differences in safety or immunogenicity in Study 24 and bioequivalence of the presentations was demonstrated by AUC.

Limitations of the Data: The 5 Phase 3 trials appropriately excluded patients who were at increased risk of developing TNF inhibitor associated AEs (e.g., patients with ongoing or recurrent infections, a recent serious infection, a known malignancy except NMSC, a history of demyelinating disease, or a history of congestive heart failure) and patients at higher risk of developing active tuberculosis (e.g., patients with a history of active tuberculosis or a history of latent tuberculosis). Thus, the incidence of TNF-inhibitor associated AEs in the clinical trials may not reflect the incidence of these reactions if golimumab were used in clinical practice. However there is an extensive post-marketing clinical experience with other TNF inhibitors and experience with golimumab would likely be similar.

Summary: In summary, the safety profile of SC golimumab in the treatment of signs and symptoms of RA, PsA, and AS appears to be consistent with the safety profile of approved TNF inhibitors. There were no unexpected safety concerns and there is no evidence to suggest that golimumab had greater risks compared to four approved TNF inhibitors. As with the four approved TNF inhibitors, the golimumab labeling should include Boxed Warnings for serious infections including tuberculosis and invasive fungal infections and Warnings for lymphoma and other malignancies and the FDA should institute a REMS with a Medication Guide, a Communication Plan, and an Assessment of REMS pertaining to the risk of serious infections including tuberculosis and invasive fungal infections.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

See Section 5.2 (Review Strategy) for the safety pools that will be used to evaluate the safety of SC golimumab in the treatment of the three indications (RA, PsA, and AS). See Table 5.1 for the design of the major safety trials for the safety analyses (the 5 Phase 3 trials) and see Table 5.2 for the design of the RA Phase 2 trial that will be supportive for the analyses of known TNF inhibitor associated AEs including infections and malignancies.

7.1.2 Adequacy of Data

Centocor's categorization of adverse events with preferred terms are consistent with the investigator's verbatim terms including the most common adverse events leading to discontinuation (e.g., sepsis, abscess, ALT increased, AST increased, hepatitis).

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

See Table 5.5 in Section 5.2 (Review Strategy) for the overview of the major **safety** evaluations of SC golimumab for the treatment of signs and symptoms of RA, PsA, and AS. In this BLA review, in addition to evaluation of the safety of golimumab in the individual study reports, the following safety data were pooled to increase precision:

1. The controlled portions of the 3 Phase 3 RA trials (Studies 5, 6, and 11) to identify safety signals in the RA population.
2. The controlled portions of the 5 rheumatology Phase 3 trials (Studies 5, 6, 11, 8, and 9) to identify safety signals across the RA, PsA, and AS populations.
3. The controlled portions and uncontrolled portions of the 5 rheumatology Phase 3 trials and the 1 Phase 2 RA trial (Studies 5, 6, 11, 8, 9, and 2) to assess for known TNF inhibitor AEs (e.g., infections and malignancies) and any unexpected AE. These controlled and uncontrolled safety data were compared to the expected background rate.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Durations and Doses

In the entire safety database of 13 completed studies of golimumab, 2894 patients received at least one dose of golimumab (2868 and 26 patients received at least one dose of SC and IV golimumab, respectively). A patient who received one dose of SC golimumab was considered to have 4 weeks of exposure to golimumab because of golimumab's 2-week long half life and golimumab's maintenance dose interval (every 4 weeks). In the 5 Phase 3 trials, 2210, 2057, and 1768 patients received at least 4, 24, and 52 weeks, respectively, of the proposed SC golimumab dose (50 mg) or a higher dose (100 mg) as of the last safety cut off date — patients may have been counted more than once.

Table 7.2.1 displays the exposure of SC golimumab in the 5 Phase 3 trials by duration as of the last safety cut-off date. The golimumab exposure in the 2 Phase 2 trials and the 6 Phase 1 studies was limited and was not included in Table 7.2.1. In the 5 Phase 3 trials, the mean (SD) number of golimumab administrations for the golimumab50 and golimumab100 groups were 15 (8) and 17 (8), respectively, and the mean (SD) cumulative golimumab dose for the golimumab50 and golimumab100 groups were 743 (383) mg and 1719 (791) mg, respectively, as of the last safety cut-off date.

An adequate number of patients were exposed to the proposed golimumab dose (50 mg every month) or higher doses in the RA, PsA, and AS populations to assess safety in these populations. The safety database fulfills the guidelines for an adequate safety database according the 2005 *Premarketing Risk Assessment* Guidance and is consistent with FDA recommendations during the pre-submission meetings regarding the golimumab development program. The size of the safety database was also reasonable given that golimumab would be the fifth approved TNF inhibitor in the United States and there were no unexpected safety signals seen.

Table 7.2.1: Number of patients who received SC study agent by duration of exposure in the controlled and uncontrolled portions of the 5 Phase 3 trials as of the last safety cutoff date[1]

Population[2]	Placebo	golimumab50			golimumab100			All golimumab doses		
		≥1 dose	≥24 weeks[3]	≥52 weeks[3]	≥1 dose	≥24 weeks[3]	≥52 weeks[3]	≥1 dose	≥24 weeks[3]	≥52 weeks[3]
RA	449	772	614	403	896	787	635	1463	1348	1099
PsA	113	248	205	194	225	168	161	394	375	355
AS	77	213	175	168	165	155	144	353	334	314
RA, PsA, & AS	639	1233	994	765	1286	1110	940	2210	2057	1768

1 Study medication assigned at randomization may have included oral MTX given weekly. The last safety data cutoff as of the 120-day Safety Update (through June 2, 2008). Patients may appear in more than one column.

2 The 3 Phase 3 RA trials were Studies 5, 6, and 11; the 1 Phase 3 PsA trial was Study 8; and the 1 Phase 3 AS trial was Study 9.

3 The number of patients exposed to golimumab for ≥ 24 weeks and ≥ 52 weeks was based on the interval between the first and the last dose of golimumab administered. Patients in whom the duration between the first and last golimumab administration was at least 20 weeks were counted as having 24 weeks of exposure and patients in whom the duration between the first and last golimumab administration was at least 48 weeks were counted as having 52 weeks of exposure. These calculations included 4 weeks of golimumab exposure after the last golimumab dose accounting for the 2 week half life of golimumab and maintenance dose interval (i.e., every 4 weeks).

Reference: Adapted from 120-Day Safety Update Report, Table 8, Page 35 and Appendix A.2, Page 120

Table 7.2.2 displays the golimumab exposure during the common, double-blind controlled periods in the 5 Phase 3 trials.

Table 7.2.2: Number of patients who received study medication by treatment group through Week 24[1] in the 5 Phase 3 trials (controlled portion of the trials)

Population[2]	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	placebo ± MTX	golimumab50 ± MTX	golimumab100[2] ± MTX	Placebo to golimumab50 ± MTX	golimumab50 to golimumab100 ± MTX
RA	449	399	691	113	56
PsA	113	146	146	51	28
AS	77	138	140	41	25
RA, PsA, & AS	639	683	977	205	109

1 Since all 5 Phase 3 studies were double-blinded and controlled through Week 24, these data represented placebo and golimumab exposure under double-blinded, controlled conditions. Patients may appear in more than one column.
2 Patients in the golimumab100 group who escaped, continued with golimumab100.
Reference: Adapted from the ISS, Table 1, Page 14; Table 3, Page 16; Table 5, Page 18; Table 7, Page 20

7.2.2 Overall Exposure at Appropriate Demographics of Target Populations

See Section 6.1.2 (Demographics and Baseline Characteristics — RA) and Section 9.4 (individual study reports) for the baseline demographics in the RA trials and see Sections 6.2.2 and 6.3.2 for the demographics in the PsA and AS trials, respectively. These demographic tables include all randomized patients; however, since there were few patients who were randomized and not treated, there are no significant differences in the demographics in the randomized and treated populations. The baseline demographics in the RA, PsA, and AS trials were typical of RA, PsA, and AS populations, respectively.

There was adequate golimumab exposure to most demographic subgroups including age (e.g., patients less than 65 years old and geriatric patients), gender (women and men) and race (Caucasians and Asians) to perform subgroup safety analyses [see Section 7.6.3 (Drug-Demographic Interactions)]. Of the 2297 treated patients in the 5 Phase 3 trials, 46 (2%) were Black (18, 11, and 17 received placebo, golimumab50, and golimumab100, respectively). Although there were few Black patients in the 5 Phase 3 trials, the racial demographics in the 5 Phase 3 trials are consistent with the racial demographics of patients with RA, PsA, and AS.

7.2.3 Special Animal and/or In Vitro Testing

According to Dr. Bond, the pharmacology and toxicology studies of golimumab were adequate to explore golimumab's potential adverse reactions [see Section 4.3 (Preclinical Pharmacology/Toxicology) for more details].

7.2.4 Routine Clinical Testing

Table 7.2.3 displays a summary of the clinical testing that was performed in the golimumab studies to elicit AEs, vital signs, laboratory parameters, and other important tests. Table 7.2.3 details the testing performed in the 5 most important trials that support the safety of SC golimumab in the treatment of RA, PsA, and AS — the 5 Phase 3 trials — and other special testing in the other Phase 1 and Phase 2 studies of golimumab in patients with RA and in healthy subjects.

The types and frequencies of safety tests used to assess AEs, vital signs, labs, and other tests were adequate to assess the safety of golimumab in the RA, PsA, and AS populations. These safety tests were adequate to evaluate the known TNF inhibitor associated AEs.