Table 9.1.19: Change from baseline of each ACR component at Week 24 in Study 5[1]

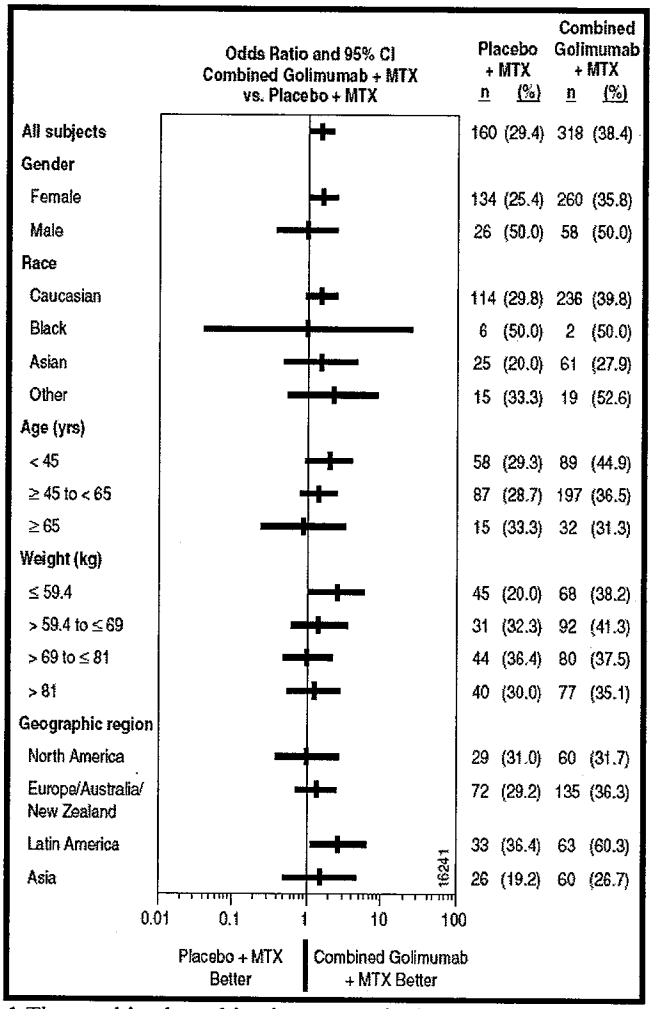
		Monotherapy Groups		Combination Groups	
		MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX
Number of swollen joints (range is 0-66)	n with measurement	151	147	152	151
	Median # of swollen joints at baseline	11	12	13	13
	Median # of swollen joints at Week 24	4	4	3	4
	Percent change from baseline at Week 24	67%	67%	76%	71%
Number of tender joints (range is 0-68)	n with measurement	151	147	152	151
	Median # of tender joints at baseline	26	25	25	26
	Median # of tender joints at Week 24	8	9	7	7
	Percent change from baseline at Week 24	57%	57%	67%	67%
Patient's assessment of pain (VAS 0-10 cm)	n with measurement	150	148	152	150
	Median pain at baseline	7	7	7	7
	Median pain at Week 24	4	4	3	3
	Percent change from baseline at Week 24	44%	38%	52%	52%
Patient's assessment of disease activity (VAS 0-10 cm)	n with measurement	151	148	152	150
	Median disease activity at baseline	6	7	6	6
	Median disease activity at Week 24	4	4	3	2
	Percent change from baseline at Week 24	37%	35%	50%	52%
Physician's assessment of disease activity (VAS 0-10 cm)	n with measurement	151	148	152	151
	Median disease activity at baseline	6	6	6	6
	Median disease activity at Week 24	2	3	2	2
	Percent change from baseline at Week 24	63%	57%	67%	64%
HAQ disability index (0-3)	n with measurement	150	146	150	150
	Median HAQ at baseline	1.63	1.75	1.50	1.63
	Median HAQ at Week 24	1.00	1.00	0.75	0.75
	Percent change from baseline at Week 24	37%	31%	44%	49%
CRP (mg/dL)	n with measurement	151	145	152	149
	CRP at baseline	1.4	1.2	1.2	1.3
	Median CRP at Week 24	0.5	0.3	0.3	0.3
	Percent change from baseline at Week 24	43%	25%	57%	63%

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 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 and then escalation by Week 20 to 20 mg)
1 The proportion of patients with improvement from baseline in each ACR component at Week 24 were 7 of 155 pre-specified other sign and symptom endpoints without multiplicity adjustments in Study 5.
Reference: Adapted from Final Study Report for Study 5, Table 3.17, Pages 433-435; Table 13, Pages 87-88, Table 14, Pages 89-90; also from JMP VISRA datasets in Study 5.

Subgroup Efficacy Analyses: Table 9.1.20 presents the subgroup efficacy analyses of the MTX monotherapy control group compared to the combined low and high dose combination groups, using the primary efficacy endpoint, by demographics. Table 9.1.21 presents the subgroup efficacy analyses of the MTX monotherapy control group compared to the combined low and high dose combination groups, using the primary efficacy endpoint, by disease duration, RF status, and baseline medication use. In these subgroup analyses, the combined low and high dose combination groups instead of the individual low and high dose combination groups to increase the sample size and because there was no evidence of a dose response between the low and high dose combination groups.

There was no clear evidence of a differential response between the combined combination groups compared to the MTX group in the proportion of ACR 50 responders at Week 24 in the demographic, disease duration, RF status, and baseline medication use subgroups.

Figure 9.1.20: Efficacy (i.e., ACR 50 responders at Week 24) of the combined combination golimumab groups[1] vs. the MTX monotherapy group by demographic subgroups in Study 5[2]

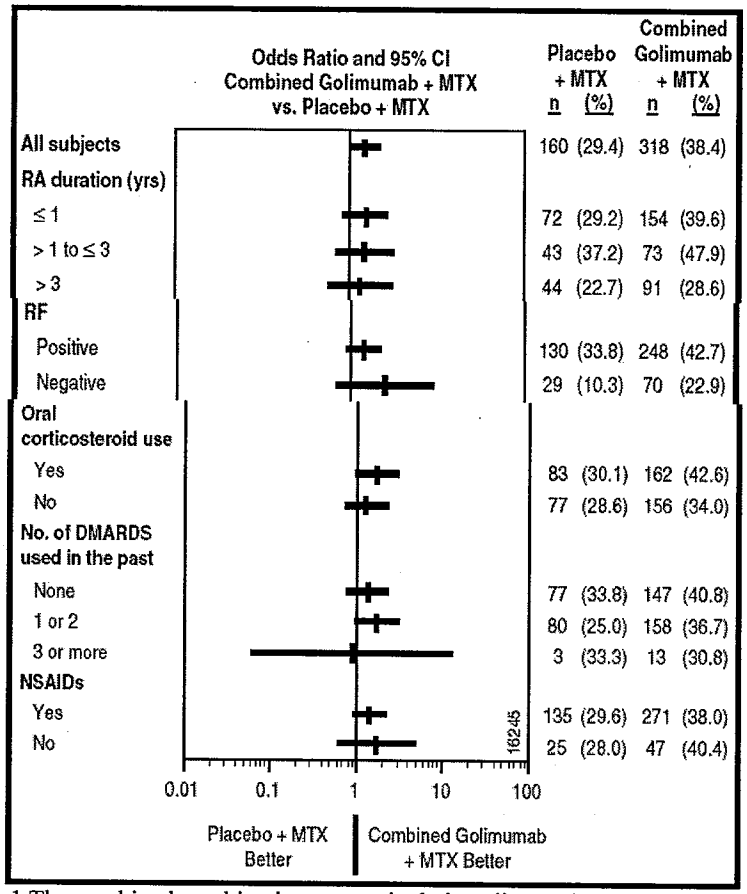


1 The combined combination groups include golimumab50 & MTX and golimumab100 & MTX. It does not include the golimumab100 monotherapy group. Centocor only proposes the use of golimumab in combination with MTX for the treatment of RA.

2 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 50 response at Week 24 and p is the proportion of patients in the placebo group with an ACR 50 response at Week 24. 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 ACR 50 response at Week 24 was the primary efficacy analysis for Study 5.

Reference: Adapted from the final study report for Study 5, Attachment 3.86, Page 544

Figure 9.1.21: Efficacy (i.e., ACR 50 responders at Week 24) of the combined combination golimumab groups[1] vs. the MTX monotherapy group by disease duration, RF status, and baseline medication use in Study 5[2]



1 The combined combination groups include golimumab50 & MTX and golimumab100 & MTX. It does not include the golimumab100 monotherapy group. Centocor only proposes the use of golimumab in combination with MTX for the treatment of RA.

2 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 50 response at Week 24 and p is the proportion of patients in the placebo group with an ACR 50 response at Week 24. 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 ACR 50 response at Week 24 was the primary efficacy analysis for Study 5.

Reference: Adapted from the final study report for Study 5, Attachment 3.90, Page 548; Attachment 3.90, Page 549

The second primary endpoint (change from baseline in vdH-S score at Week 52): Data on this radiographic endpoint was not included in Centocor's original BLA submission (24-week data).

b(4)

Exposure: Table 9.1.22 displays the exposure of SC golimumab through Week 24 and Week 52 and the exposure of PO MTX through Week 24 in Study 5. MTX was one of the study medications in 3 out of the 4 treatment groups in Study 5.

Table 9.1.22: SC agent (golimumab or placebo) and PO MTX exposure through Week 24 and SC agent exposure through Week 52 in Study 5[1]

	Treatment Groups Assigned at Randomization				Escape Treatment Groups		
	MTX (n=159)	Golimumab100 (n=157)	Golimumab50 & MTX (n=158)	Golimumab100 & MTX[2] (n=160)	MTX to Golimumab50 & MTX (n=28)	Golimumab100 to Golimumab100 & MTX (n=22)	Golimumab50 & MTX to Golimumab100 & MTX (n=20)
Oral MTX exposure in through Week 24							
Mean (SD) cumulative PO MTX dose, mg	408 (78)	1 (6)	402 (75)	400 (84)	—	—	—
Mean weekly PO MTX dose, mg	17 mg/week	0 mg/week	17 mg/week	17 mg/week	—	—	—
SC study agent exposure in through Week 24							
Mean duration of follow-up	23.4 weeks	23.7 weeks	24.0 weeks	23.5 weeks	—	—	—
Mean # of SC administrations	5.8	5.7	5.8	5.8	—	—	—
Mean (SD) cumulative dose[3]	0 (0) mg	575 (81) mg	291 (33) mg	575 (87) mg	—	—	—
SC study agent exposure in through Week 52							
Mean duration of follow-up	45.1 weeks	46.0 weeks	47.2 weeks	49.6 weeks	23.6 weeks	23.9 weeks	22.7 weeks
Mean # of SC administrations	11.1	11.2	11.5	12.0	5.5	5.9	5.7
Mean (SD) cumulative dose[3]	0 (0) mg	1116 (303) mg	574 (143) mg	1190 (271) mg	273 (55) mg	591 (29) mg	574 (115) mg

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 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 and then escalation by Week 20 to 20 mg)

1. Treated population (patients who received one SC dose of study agent) was the pre-specified statistical population for the safety analyses. The controlled portion of Study 5 was through Week 52. Patients may appear in more than one column. Database locks occurred at Weeks 24 and 52.
2. Patients in the Golimumab100 & MTX group who escaped at Week 28 continued their treatment (i.e., golimumab100 & MTX). This column contains data from patients who escaped and patients who did not escape.
3. Mean cumulative golimumab dose.

Adapted from 120-Day Safety Update report, Appendix A.1, Page 119; and from the Final Study Report for Study 5, Table 24, Page 129; Table 25, Page 129; Table 4.1 Pages 556-560

Safety: See Sections 7.3, 7.4, 7.5, and 7.6 for a discussion of the pooled safety results of the 5 Phase 3 trials.

Table 9.1.23 presents the major safety results of Study 5 through Week 52 [n (%) of patients who died, had SAEs, DAEs, and/or AEs]. See Table 7.3.3 in Section 7.3.1 for details of the narratives of the 3 golimumab-treated patients who died through Week 52 in Study 5. There were no meaningful

differences in the proportion of patients who had SAEs in the treatment groups. A higher proportion of patients in the combination groups had DAEs compared to the MTX group.

Table 9.1.23: Patients with ≥ 1 death, non-fatal SAE, DAE, and AE through Week 52 in Study 5[1]

	Treatment Groups Assigned at Randomization				Escape Treatment Groups		
	MTX	golimumab100 monotherapy	golimumab50 & MTX	golimumab100[2] & MTX	MTX to golimumab50 & MTX	golimumab100 to golimumab100 & MTX	golimumab50 & MTX to golimumab100 & MTX
Treated patients	159	157	158	160	28	22	20
Mean duration of therapy	45.1 weeks	46.0 weeks	47.2 weeks	49.6 weeks	23.6 weeks	23.9 weeks	22.7 weeks
Mean # SC administrations	11.1	11.2	11.5	12.0	5.5	5.9	5.7
Deaths[3]	0 (0%)	0 (0%)	1 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
SAEs[4]	22 (14%)	13 (8%)	18 (11%)	21 (13%)	4 (14%)	1 (5%)	0 (0%)
DAEs[4]	6 (4%)	7 (5%)	9 (6%)	16 (10%)	2 (7%)	0 (0%)	1 (5%)
AEs[5]	134 (84%)	127 (81%)	145 (92%)	147 (92%)	19 (68%)	16 (73%)	15 (75%)

1 Since Study 5 was double-blinded and MTX-controlled through Week 52, these data represented study agent exposure under double-blinded, controlled conditions. Patients may appear in more than one column.
2 Patients in the golimumab100 & MTX combination group who escaped, continued with golimumab100.
3 For details on all the deaths that occurred in Study 5 see Section 7.3.1 (Deaths)
4 There were few SAEs and DAE preferred terms that occurred ≥ 2 in any treatment group through Week 52 in Study 5. Therefore, analysis of SAE and DAE preferred terms was performed on the pooled 5 Phase 3 trials (see Table 7.3.6 in Section 7.3.2 for the pooled SAE preferred terms and see Table 7.3.7 in Section 7.3.3 for the pooled DAE preferred terms.
5 For details on the types of AEs in Study 5 see Table 9.1.24 in this study report.
Adapted from the 120-Day Safety Update, Appendix A.10, Pages 284-292, Appendix A.15, Pages 316-322; Table 10, Page 42, Appendix A.4, Page 156

Table 9.1.24 displays the most common AEs through Week 52 in Study 5. The combined combination golimumab groups had greater proportion of infection AEs (e.g., URI, nasopharyngitis, UTI), increased liver enzymes (increased ALT and AST), injection site erythema, and gastrointestinal-related AEs (nausea, dyspepsia, upper abdominal pain, vomiting) than the MTX control group.

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Table 9.1.24: AEs (frequency ≥ 5% in any golimumab group) by MedDRA preferred term through Week 52 in Study 5[1]

	Treatment Groups Assigned at Randomization				Escape Treatment Groups		
	MTX (n=159)	Golimumab100 (n=157)	Golimumab50 & MTX (n=158)	Golimumab100 & MTX[2] (n=160)	MTX to Golimumab50 & MTX (n=28)	Golimumab100 to Golimumab100 & MTX (n=22)	Golimumab50 & MTX to Golimumab100 & MTX (n=20)
Mean duration of follow-up	45.1 weeks	46.0 weeks	47.2 weeks	49.6 weeks	23.6 weeks	23.9 weeks	22.7 weeks
Mean # of SC administrations	11.1	11.2	11.5	12.0	5.5	5.9	5.7
n (%) of patients with ≥ 1 AE	134 (84%)	127 (81%)	145 (92%)	147 (92%)	19 (68%)	16 (73%)	15 (75%)
ALT increased	11%	6%	20%	12%	0%	9%	5%
Nausea	17%	8%	18%	23%	7%	9%	5%
AST increased	6%	4%	15%	8%	0%	5%	5%
URI	13%	11%	13%	16%	11%	5%	5%
Nasopharyngitis	6%	8%	9%	8%	7%	9%	0%
Dyspepsia	8%	6%	9%	6%	4%	5%	0%
Cough	9%	7%	7%	6%	4%	9%	0%
Abdominal pain upper	3%	5%	7%	4%	4%	0%	0%
Diarrhoea	9%	4%	7%	4%	4%	9%	5%
Bronchitis	9%	6%	6%	7%	11%	0%	0%
Hypertension	4%	4%	6%	6%	7%	0%	15%
Vomiting	4%	2%	6%	6%	11%	0%	6%
Rash	6%	5%	6%	5%	4%	0%	0%
Back pain	5%	5%	6%	4%	0%	0%	0%
UTI	3%	2%	6%	4%	4%	0%	0%
Sinusitis	4%	3%	6%	3%	4%	5%	10%
Headache	8%	8%	5%	9%	14%	0%	0%
Abdominal pain	4%	2%	5%	3%	0%	0%	5%
Pharyngo-laryngeal pain	3%	3%	5%	3%	4%	5%	0%
Influenza	8%	4%	4%	7%	4%	0%	0%
Injection site erythema	0%	8%	4%	6%	4%	5%	0%
Fatigue	6%	6%	4%	6%	0%	0%	0%
Insomnia	1%	5%	3%	5%	0%	0%	0%
Pyrexia	2%	3%	3%	5%	0%	0%	0%

Adapted from the 120-Day Safety Update report, Table 10, Pages 42-45

Table 9.1.25 displays the AEs of special interest (i.e., malignancies, infections) through Week 52 in Study 5. There was no significant difference in the proportion of patients who had a neoplasm AE or neoplasm SAE in the treatment groups. There was no significant difference between the proportion of proportion of patients who had an Infection AE or Infection SAE in the MTX monotherapy group and the proposed golimumab dose regimen (50 mg with concomitant MTX). The higher dose golimumab combination group had greater proportions of patients with an Infection AE or Infection SAE

compared to the MTX control group. This suggests that the lower dose golimumab combination regimen may safer than the higher dose combination regimen.

Table 9.1.25: Patients with ≥ 1 AE of special interest (i.e., malignancies, infections) through Week 52 in Study 5[1]

	Treatment Groups Assigned at Randomization				Escape Treatment Groups		
	MTX	golimumab100 monotherapy	golimumab50 & MTX	golimumab100[2] & MTX	MTX to golimumab50 & MTX	golimumab100 to golimumab100 & MTX	golimumab50 & MTX to golimumab100 & MTX
Treated patients	159	157	158	160	28	22	20
Mean duration of therapy	45.1 weeks	46.0 weeks	47.2 weeks	49.6 weeks	23.6 weeks	23.9 weeks	22.7 weeks
Mean # SC administrations	11.1	11.2	11.5	12.0	5.5	5.9	5.7
Neoplasms							
Neoplasm AEs[3]	6 (4%)	5 (3%)	5 (3%)	4 (3%)	2 (%)	0 (0%)	0 (0%)
Neoplasm SAEs[3]	3 (2%)	0 (0%)	3 (2%)	1 (1%)	1 (4%)	0 (0%)	0 (0%)
NMSC	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
All Malignancies except NMSC	2 (1%)	0 (0%)	2 (1%)	1 (1%)	1 (4%)	0 (0%)	0 (0%)
Infections							
Serious Infections[3]	6 (4%)	3 (2%)	3 (2%)	12 (8%)	2 (7%)	1 (5%)	0 (0%)
Infection AEs[4]	81 (51%)	77 (49%)	81 (53%)	89 (56%)	14 (50%)	7 (32%)	4 (20%)
URI	21 (13%)	17 (11%)	21 (13%)	26 (16%)	3 (11%)	1 (5%)	1 (5%)
Nasopharyngitis	9 (6%)	12 (8%)	14 (9%)	12 (8%)	2 (7%)	2 (9%)	0 (0%)
Bronchitis	15 (9%)	9 (6%)	10 (6%)	11 (7%)	3 (11%)	0 (0%)	0 (0%)
Influenza	12 (8%)	6 (4%)	6 (4%)	11 (7%)	1 (4%)	0 (0%)	0 (0%)
UTI	5 (3%)	3 (2%)	10 (6%)	7 (4%)	1 (4%)	0 (0%)	0 (0%)
Sinusitis	7 (4%)	4 (3%)	9 (6%)	5 (3%)	1 (4%)	1 (5%)	2 (10%)

1 Since Study 5 was double-blinded and MTX-controlled through Week 52, 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 & MTX combination group who escaped, continued with golimumab100.

3 Neoplasm AEs were AEs in the neoplasms benign, malignant, and unspecified SOC. Neoplasms SAEs were SAEs in the neoplasms benign, malignant, and unspecified SOC. Serious Infections were SAEs in which the investigator stated was an infection. The serious infections category includes MedDRA several system organ classes (SOCs) including, but not limited to, Infections and Infestations.

4 Infections AEs were AEs that were identified as infections by the investigators. Preferred terms were listed below with a frequency of ≥ 5% in any golimumab treatment group.

Adapted from the 120-Day Safety Update, Appendix A.10, Pages 284-292, Appendix A.15, Pages 316-322; Table 10, Page 42, Appendix A.4, Page 156; also adapted from JMP dataset in 120-Day Safety Update of Study 5 through Week 52.

9.4.2 Study C0524T06 (Study 6) – RA (MTX non-responders)

The following description of the protocol for Study C0524T06 (Study 6; GO FORWARD) is based on amendment 2 of the protocol (dated March 22, 2007) and amendment 1 of the SAP (dated April 9, 2007). See Table 9.2.1 for the dates of all amendments to the protocol and SAP for Study 6.

In Study 6, the first patient consented on December 19, 2005 and the last patient completed Week 24 on September 17, 2007. The final protocol amendment (amendment 2) and the final SAP (amendment 1) occurred prior to the 24-week database lock in Study 6. In amendment 2 of the protocol, there were no significant changes to the study conduct of Study 6 up to 24 weeks compared to the original protocol. Similarly, there were no significant changes to statistical methods up to 24 weeks in amendment 1 of the SAP compared to the original SAP.

Table 9.2.1: Amendments to the Study 6 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	August 25, 2005
	Amendment 1 to Protocol	February 8, 2007
	Amendment 2 to Protocol[1]	March 22, 2007[1]
SAP	Original SAP	December 19, 2006
	Amendment 1 to SAP[2]	April 9, 2007[2]

Date of 24-week data base lock was on September 17, 2007 or after this date.
1 Amendment 2 to the Protocol was the last amendment before the first data base lock.
2 Amendment 1 to the SAP was the last amendment before the first data base lock.
Adapted from the final study report and SAP for Study 6

Title: Study 6 (GO FORWARD) is entitled, "A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy"

Objectives: The primary objectives of this study are to assess the efficacy of golimumab in patients with active RA despite MTX therapy as measured by the reduction of the signs and symptoms of RA at Week 14 and the improvement in physical function at Week 24. The secondary objectives are to assess the safety, the effects of golimumab on structural damage and quality of life, and the population PK of golimumab in patients with active RA despite MTX therapy.

Overall Design: Randomized, DB, placebo-control, multi-center, global, 4-arm, 5-year Phase 3 trial of golimumab in patients with active RA despite MTX therapy and have never received a TNF inhibitor, rituximab, natalizumab, or a cytotoxic agent. Patients must have been treated with and tolerated MTX at a dose of at least 15 mg/week for at least 3 months prior to screening, and have a MTX dose of ≥ 15 mg/week and ≤ 25 mg/week and stable for at least 4 weeks prior to screening. Patients may be taking stable doses of NSAIDs and corticosteroids equivalent to ≤ 10 mg prednisone/day. There will be three main treatment periods in Study 6 (see Figure 9.2.2).

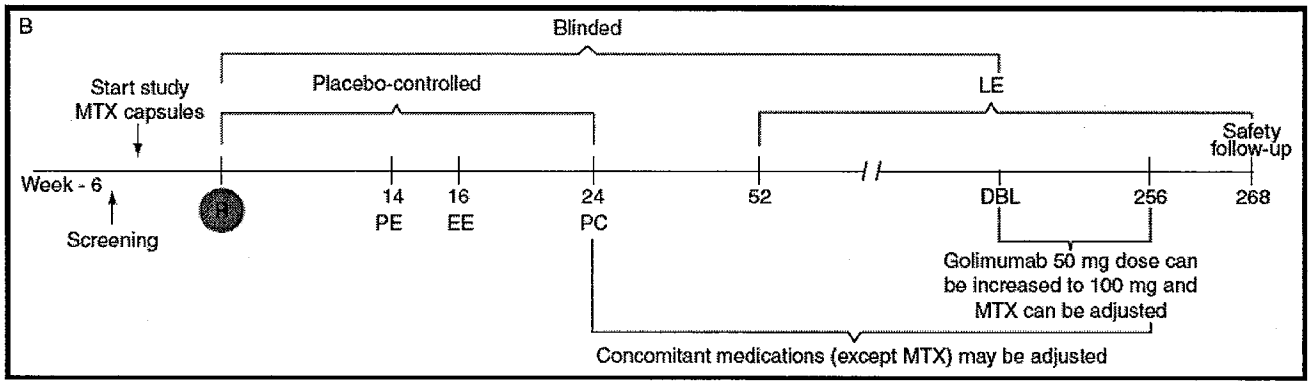
1. DB, placebo-controlled, non-crossover period with two parts:

   - 16-week period from Week 0 to Week 16

- 8-week period from Week 16 to Week 24 (where at Week 16 patients could enter into an escape phase for lack of efficacy)

2. DB, dose-ranging control period from Week 24 to Week 52
3. 4-year, LE period from Week 52 to Week 256 The initial part of the LE period will be DB but the time period after the Week 52 database lock will be open-label (the Week 52 database lock will occur when the last patient completes the one-year controlled portion of the study).

Figure 9.2.2: Study 6 schema

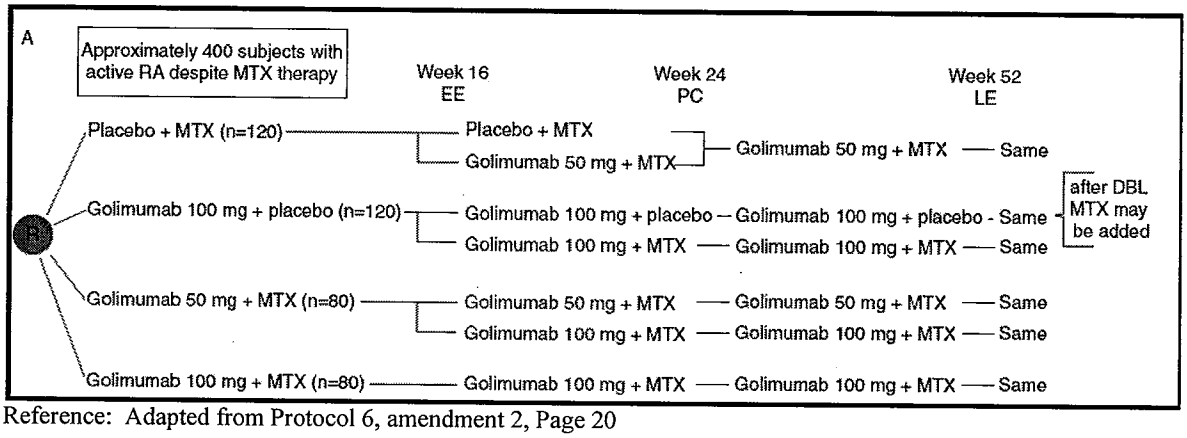


R = Randomization; PE = Primary endpoint; PC = Placebo crossover (background MTX group crosses over to receive golimumab); DBL = database lock; LE long-term extension
EE = early escape (patient having < 20% improvement in both tender & swollen joint counts)
Reference: Adapted from Protocol 6, amendment 2, Page 20

Eligibility Criteria: The eligibility criteria were identical to the eligibility criteria in Study 5 (see Table 9.1.3) except that in Study 6, patients with RA must "have been treated with and tolerated MTX at a dose of at least 15 mg/week for at least 3 months prior to screening, and have a MTX dose of ≥ 15 mg/week and ≤ 25 mg/week and stable for at least 4 weeks prior to screening." In contrast, Study 5 included patients who were MTX-naïve (i.e., have not received more than 3 weekly doses of MTX for RA at any time). As in Study 5, patients in Study 6 must have never received a TNF inhibitor, rituximab, natalizumab, or a cytotoxic agent and patients may be taking stable doses of NSAIDs and corticosteroids equivalent to ≤ 10 mg prednisone/day.

Treatments: Patients will receive study treatment during the DB and LE periods (see Figure 9.2.3). Golimumab will be supplied as a sterile liquid (liquid in a vial or LiV) for SC injection and once available, golimumab may also be supplied as a sterile liquid for SC injection in prefilled syringe (PFS).

Figure 9.2.3: Treatments in Study 6[1]



Reference: Adapted from Protocol 6, amendment 2, Page 20

DB, Placebo-Control Period: Patients will be randomized 3:3:2:2 to 1 of the following 4 treatment groups: Groups 1, 2, 3, and 4 (see Table 9.2.4 and Figure 9.2.3).

Table 9.2.4: Treatment groups at randomization in the DB, placebo-control period (Week 0 to 24) in Study 6[1]

Group #	Dosing
Group 1	Oral MTX once weekly[2] (this is the identical treatment as the treatment received prior to enrollment)[3]
Group 2	golimumab 100 mg SC once every 4 weeks[3]
Group 3	golimumab 50 mg SC once every 4 weeks and oral MTX once weekly[2] (this is the identical treatment as the treatment received prior to enrollment)[3]
Group 4	golimumab 100 mg SC once every 4 weeks and oral MTX once weekly[2] (this is the identical treatment as the treatment received prior to enrollment)[3]

1 Patients who receive golimumab will start at Week 0 then every 4 weeks until Week 20. Patients who receive MTX will start at Week 0 and then once weekly until Week 23. Patients who escape at Week 16 may receive different treatment from Weeks 16 to Week 20 (see Table 9.2.5). At Week 24, patients in Group 1 (MTX monotherapy) will cross over to golimumab 50 mg once every 4 weeks (see Table 9.2.6).
2 The MTX dose will be identical to the MTX dose prior to enrollment, between 15-25 mg orally once weekly.
3 Patients may take stable doses of concomitant NSAIDs and/or corticosteroids equivalent to ≤ 10 mg prednisone/day during the study.
Reference: Adapted from Protocol 6, amendment 2, Page 21

At Week 16 during the DB Period, any patient who has < 20% improvement from baseline in both swollen and tender joint counts will enter early escape in a double-blinded fashion (see the treatments for the patients who enter escape in Table 9.2.5 and Figure 9.2.3). Patients who do not enter early escape will continue the treatment assigned at randomization (see Table 9.2.5 and Figure 9.2.3).

Table 9.2.5: Treatments for patients who enter escape at Week 16[1] in Study 6

Group #	Treatment prior to escape	Treatment during escape
Group 1	Background MTX	**Add golimumab 50 mg** SC every 4 weeks & continue background MTX
Group 2	golimumab 100 mg SC every 4 weeks	Continue golimumab 100 mg SC every 4 weeks & **add MTX** once weekly (dose will be equivalent to the dose prior to enrollment, which is between 15-25 mg once weekly)[2]
Group 3	golimumab 50 mg SC every 4 weeks & background MTX	**Increase golimumab to 100 mg** SC every 4 weeks & continue background MTX[2]
Group 4	golimumab 100 mg SC every 4 weeks & background MTX	Continue golimumab 100 mg SC every 4 weeks & background MTX (no change in treatment)[2]

1 For patients who enter escape at Week 16, they will be treated in a double-blind fashion at Week 16 and Week 20. All groups will receive golimumab every 4 weeks (i.e., at Week 16 and Week 20).
2 Patients may take stable doses of concomitant NSAIDs and/or corticosteroids equivalent to ≤ 10 mg prednisone/day during the study.
Reference: Adapted from Protocol 6, amendment 2, Page 21-22

DB, Dose-Ranging Control Period: During the DB, dose-ranging control period, patients in Group 1 (i.e., background MTX monotherapy) will crossover at Week 24 to golimumab 50 mg SC once every 4 weeks and continue their MTX. Patients in Groups 2, 3, and 4 will continue their treatments as they received in the DB, placebo-control period (see Table 9.2.6 and Figure 9.2.3). Concomitant medications, except MTX and golimumab, may be adjusted during this period.

Table 9.2.6: Treatments during the DB, dose-ranging control period from Week 24 to Week 52 in Study 6[1]

Group #		Treatment during Week 24 to Week 52
Group 1	For all patients	Cross over to continue background weekly oral MTX and **add golimumab 50 mg** SC mg every 4 weeks until Week 52.
Group 2	For patients who did not escape	Continue golimumab 100 mg SC every 4 weeks (no change)
	For patients who entered escape	Continue golimumab 100 mg SC every 4 weeks and continue background MTX (no change)
Group 3	For patients who did not escape	Continue golimumab 50 mg SC every 4 weeks and continue background MTX (no change).
	For patients who entered escape	Continue golimumab 100 mg SC every 4 weeks and continue background MTX (no change)
Group 4	For all patients	Continue golimumab 100 mg SC every 4 weeks and continue background MTX (no change)

1 All groups will receive golimumab starting at Week 24 every 4 weeks until Week 48. For the groups receiving MTX, MTX will be given orally once weekly starting at Week 24 to Week 53.
Reference: Adapted from Protocol 6, amendment 2, Page 21-22

LE Period: Treatment during the Long-Term Extension (LE) Period will start at Week 52 and continue through Week 252 (see Table 9.2.7 and Figure 9.2.3).

Table 9.2.7: Treatments during the Long-Term Extension Period from Week 52 to 252 in Study 6[1]

Group #		Treatment during Week 52 to Week 252
Group 1	For all patients	Continue background weekly oral MTX and continue golimumab 50 mg SC mg every 4 weeks **(option to increase golimumab to 100 mg SC once every 4 weeks).**
Group 2	For patients who did not escape	Continue golimumab 100 mg SC every 4 weeks **(option to add MTX)**
	For patients who entered escape	Continue golimumab 100 mg SC every 4 weeks and continue background MTX
Group 3	For patients who did not escape	Continue golimumab 50 mg SC every 4 weeks and continue background MTX **(option to increase golimumab to 100 mg SC once every 4 weeks).**
	For patients who entered escape	Continue golimumab 100 mg SC every 4 weeks and continue background MTX
Group 4	For all patients	Continue golimumab 100 mg SC every 4 weeks and continue background MTX

1 All groups will receive golimumab starting at Week 52 every 4 weeks until Week 252. The blind will be maintained in LE Period until after the last patient finishes the 52-week evaluations and the 52-week database is locked. Therefore, during the initial part of LE, the treatments will be double-blinded and patients in Group 2 who did not escape may receive sham MTX (placebo) oral pills. After the 52-database is locked, the dose of MTX can also be adjusted. After the Week 52 evaluations have been completed, the dosing regimens of concomitant therapy with NSAIDs, corticosteroids, and/or other analgesics may be adjusted.
Reference: Adapted from Protocol 6, amendment 2, Page 22-23

Concomitant Medication: The procedures for the use of concomitant medications in Studies 5 and 6 are identical (see Concomitant Medication in Study 5 for more details).

Study Monitoring and Evaluations: See Table 9.2.8 for the schedule of procedures and evaluations in Study 6. All post-baseline visits through Week 52 must have occurred within ± 7 days except the Week 12, 14, and 16 visits must have occurred within ± 3 days.

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Table 9.2.8: Schedule of procedures and evaluations through Week 52 in Study 6

Assessments[a]	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 14[b]	Wk 16	Wk 20	Wk 24[b]	Wk 28	Wks 32-48[c]	Wk 52
Consent	X											
Demography/medical history	X											
Physical examination	X								X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Weight	X					X			X			X
Chest x-ray[d,e]	X											
Tuberculin skin test[e]	X											
QuantiFERON-TB Gold test[e]	X											
TB evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Review of entry criteria	X	X										
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
IVRS notification of tender & swollen joint counts		X					X					
Study agent injection		X	X	X	X		X	X	X	X	X	X[f]
Study agent injection-site evaluation[g]		X	X	X	X	X	X	X	X	X	X	X
RA evaluations[a]	X[j]	X	X	X	X	X	X	X	X	X	X	X
SF-36		X				X			X			X
HEcon		X		X			X		X			X
FACIT-F		X				X			X			
Pain[j]		X				X						
Radiographs of hands and feet[k]	X						X[l]		X[m]			X
MRI[k,n]	X				X				X[t]			X
AE review[o]	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[p]	X											
Routine laboratory analyses	X	X	X	X		X		X	X	X	X[q]	X
CRP	X	X	X	X	X	X	X	X	X	X	X	X
ESR	X[r]	X[r]				X			X			X
Rheumatoid factor	X					X						
Anti-CCP antibodies	X					X						
Fasting serum lipids		X				X						X
Fasting serum glucose		X				X						X
HbA1c		X			X				X			X
ANA/anti-dsDNA antibodies		X				X						X
Golimumab concentration		X	X	X	X	X	X	X	X			X
Population PK						←X[s]→						
Serum-based PD biomarkers[n]		X	X			X			X			
Cell-based PD biomarkers[n]		X	X				X					
Protein profiling[n]		X	X			X						
Antibodies to golimumab		X							X			X
Cardiovascular biomarkers		X				X			X			X
Anemia markers		X				X						

a All assessments are to be completed prior to study agent administration, unless otherwise specified.
b Primary endpoint visits.
c Assessments during this period are to be performed every 4 weeks, unless otherwise specified.
d May be taken within 3 months prior to Week 0.

e Also performed at any time during the study if TB is suspected.
f Long-term extension starts with the Week 52 study agent injection.
g Also performed for at least 30 minutes after study agent administration.
h RA evaluations include: joint assessment, pain assessment, Patient's and Physician's Global Assessments of Disease Activity, and HAQ at Weeks 0 to 52. In addition, the duration of morning stiffness is also evaluated at Week 0.
i Only the duration of morning stiffness and joint assessment are performed at screening.
j Assessed using the pain intensity scale of the BPI.
k The initial assessment may be performed after the screening visit, but must be completed within 4 weeks before first study agent administration.
l Performed only for patients who enter early escape.
m Performed only for patients who do not enter early escape.
n Performed at selected sites.
o Also performed for 30 minutes after study agent administration.
p May be repeated at any time at the discretion of investigator or patient.
q Performed at Weeks 36 and 44 during this period.
r Performed at screening or Week 0.
s One additional sample for serum golimumab concentration will be collected from all patients at any time between Weeks 14 and 20 other than at the time of the Week 14, Week 16, and Week 20 visits; this sample must be collected at least 24 hours prior to or after a study agent injection.
t Week 24 MRI should be performed within 7 days before the injection of study agent.
Reference: Adapted from Protocol 6, amendment 1, Attachment 1, Pages 72-73

Efficacy Endpoints:

Co-Primary Efficacy Endpoints: The co-primary efficacy endpoints are the proportion of patients with an ACR 20 response at Week 14 and the improvement in HAQ at Week 24.

ACR 20 Response at Week 14: Patients will be classified as having achieved an ACR 20 response at Week 14 if both of the following is achieved at Week 14:

1. An improvement of $\geq$ 20% from baseline in both the swollen joint count (66 is the maximum number of swollen joints) **and** tender joint count (68 is the maximum number of tender joints); and
2. An improvement of $\geq$ 20% from baseline in $\geq$ 3 of the following 5 assessments:

2.6. Patient's assessment of pain using a Visual Analog Scale (VAS)
2.7. Patient's global assessment of disease activity, using a VAS
2.8. Physician's global assessment of disease activity, using a VAS
2.9. Patient's assessment of physical function as measured by the HAQ disability index
2.10. CRP

Improvement in HAQ at Week 24: The baseline HAQ disability index score minus the Week 24 HAQ disability index score (positive values indicate less disability and negative values indicate more disability). The HAQ disability index is composed of the following 8 categories: dressing & grooming (C1), arising (C2), eating (C3), walking (C4), hygiene (C5), reach (C6), grip (C7), and activities (C8). Each of the categories has $\geq$ 2 component questions and for each of the components, patients are asked to record the amount of difficulty they may have in performing various activities with the following 4 responses: without ANY difficulty = 0, with SOME difficulty = 1, with MUCH difficulty = 2, and UNABLE to do = 3. Each of the component scores may be adjusted if the patient used an aid, device,

or assistance. The highest score recorded by the patient for any component question determines the score for that category. The HAQ is calculated as the sum of the category scores divided by the number of categories answered. The HAQ is not computed if the patient does not have scores for at least 6 of the 8 categories.

Secondary Efficacy Endpoints: The 4 secondary efficacy endpoints are the following (without a pre-specified order):

1. ACR 20 response at Week 24
2. Improvement from baseline in HAQ at Week 14
3. Disease Activity Score (DAS) 28 (using CRP) response at Week 14 [for the definition of DAS 28 (CRP) response see the secondary endpoints in Study 5]
4. Change from baseline in vdH-S score (for the definition of vdH-S score see the secondary endpoints in Study 5) at Week 24.

107 Other Pre-Specified Endpoints Related to Signs and Symptoms: The following are the 107 other pre-specified endpoints related to signs and symptoms:

ACR Response Endpoints:

1. 6 endpoints: proportion of patients who achieve an ACR 50, ACR 70, and ACR 90 response at Week 14 and Week 24.
2. 28 endpoints: proportion of patients who achieve an ACR 20, ACR50, ACR70, and ACR90 response over time (i.e., at Weeks 4, 8, 12, 14, 16, 20, and 24).
3. 2 endpoints: ACR-N index of improvement at Week 14 and 24 (for the definition of ACR-N improvement see Table 9.1.9 in the study report for Study 5).

ACR Component Endpoints:

4. 14 endpoints: percent improvement from baseline in each of the 7 ACR components at Week 14 and Week 24
5. 28 endpoints: percent improvement from baseline in swollen joint counts, tender joint counts, HAQ, and CRP at each visit through Week 24 (7 visits).

Change in DAS28 Endpoints:

6. 14 endpoints: the change from baseline in DAS 28 (CRP) at each visit through Week 24 (7 visits) and the change in baseline in DAS 28 (ESR) at each visit through Week 24 (7 visits). For the formulas for the DAS 28 (CRP) and the DAS 28 (ESR), see Table 9.1.10 in the study report for Study 5.

DAS Response and Remission Endpoints:

7. 2 endpoints: proportion of patients with DAS 28 response (ESR) at Week 14 and Week 24.
8. 1 endpoint: proportion of patients who achieve DAS 28 (CRP) response at Week 24
9. 4 endpoints: proportion of patients with DAS 28 (CRP) remission at Week 14 and Week 24 and the proportion of patients with DAS 28 (ESR) remission at Week 14 and Week 24.

ACR Response by PK Endpoints:

10. 8 endpoints: Efficacy by PK analysis of the golimumab monotherapy group compared to the combined combination groups. The proportion of patients who achieve an ACR 20 response at Week 14 who have a trough serum golimumab concentration of < 0.2 μg/mL, ≥ 0.2 to < 1 μg/mL, ≥ 1 to < 2 μg/mL, and ≥ 2 μg/mL and the proportion of patients who achieve an ACR 50 response at Week 24 who have a trough serum golimumab concentration of <0.2 μg/mL, ≥ 0.2 to < 0.1 μg/mL, ≥ 1.0 to < 2.0 μg/mL, and ≥ 2.0 μg/mL. The 4 categories of trough serum golimumab concentrations can be changed based on observed PK data.

Other Pre-Specified Endpoints: There were numerous pre-specified endpoints relating to joint structural damage, maintenance of improvement in HAQ through Week 104, cardiovascular (e.g., cardiovascular adverse reactions, cardiovascular markers), MRI of the wrists and MCPs, SF-36, Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), the Brief Pain Inventory (BPI).

Statistics:

Populations: The pre-specified populations in Study 5 and 6 were identical (see Populations in Study 5 for more details).

Database Locks: The 4 database locks in Study 6 will occur at Weeks 24, 52, 104, and 268 after all patient evaluations through Weeks 24, 52, 104, and 268, respectively.

Methods for the ACR20 and HAQ Co-Primary Efficacy Endpoints: To control Type I error, the statistical analysis on 2 co-primary endpoints will be performed sequentially in the following order:

1. Proportion of patients with an ACR 20 response at Week 14
2. Improvement in HAQ at Week 24

There will be three-tiered testing for the first co-primary efficacy endpoint (i.e., ACR 20 response at Week 14):

1. The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) chi-square test, will be between the combined low and high dose combination groups (i.e., golimumab 50 & MTX and golimumab 100 & MTX, respectively) versus the MTX monotherapy group.
2. If this is significant, a comparison (for superiority), using the same statistical procedure above with $\alpha = 0.05$, between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX will be performed.
3. If "positive tests results for the analysis" presented above are achieved then a superiority analysis, using a 2-sided ($\alpha = 0.05$) chi-square test, between the golimumab and MTX monotherapy groups will be performed.

The second co-primary efficacy endpoint (improvement in HAQ at Week 24) will only be considered if the first co-primary endpoint (i.e., ACR 20 response at Week 14) is positive. There will be three-tiered testing for the second co-primary efficacy endpoint (i.e., improvement in HAQ at Week 24):

1. The primary statistical comparison (for superiority), using a 2-sided analysis of variance on the van der Waerden normal scores ($\alpha = 0.05$), will be between the combined low and high dose combination groups (i.e., golimumab 50 & MTX and golimumab 100 & MTX, respectively) versus the MTX monotherapy group.
2. If this is significant, a comparison (for superiority), using the same statistical procedure above with $\alpha = 0.05$, between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX will be performed.
3. If "positive tests results for the analysis" presented above are achieved then a superiority analysis, using the same statistical procedure above with $\alpha = 0.05$, between golimumab monotherapy group and MTX monotherapy group will be performed.

According to the SAP a positive trial constitutes a positive test result for the first co-primary efficacy endpoint (i.e., ACR 20 response at Week 14). A positive test result for this endpoint is defined as a statistically significant global test (the combined low and high dose combination groups versus MTX **and** at least one statistically significant pair-wise test (low-dose combination group with MTX and the high-dose combination group with MTX).

Handling of Treatment Failure, Dropouts, and Missing Data for the ACR 20 at Week 14 Primary Efficacy Endpoint: Patients, who meet ≥ 1 of the following treatment failure criteria prior to Week 14, will be considered to not have achieved an ACR 20 response at Week 14:

1. Initiate DMARDs, systemic immunosuppressives, or biologics for RA;
2. Discontinue study agent injections due to an unsatisfactory therapeutic effect;
3. Initiate treatment with oral corticosteroids for RA, increase the dose of oral corticosteroids for RA above the baseline dose, or receive IV or IM corticosteroids for RA; or
4. Increase the dose of oral study agent above the baseline dose for RA.

Patients with missing data for all of the ACR components at Week 14 will be considered as ACR 20 non-responders at Week 14. If patients have missing data but have data for ≥ 1 ACR component at Week 14, the following rules will be applied in the specified order:

1. For any ACR component, if **all the component values** are missing from baseline through Week 14, the percent improvement from baseline at Week 14 will be imputed with 0%.
2. For any ACR component, if the **component value at Week 14** is missing, the missing component will be replaced by the last non-missing observation (LOCF).
3. For any ACR component, if the **component value at baseline is missing**, the median component value of all patients at baseline will be assigned.

For 4 of the 6 ACR components (i.e., patient's assessment of pain, global disease activity, physical function, and the physician's global assessment of disease activity), impute the percent improvement from baseline with 0 if the post-baseline value is 0, otherwise if the post-baseline value is greater than 0, calculate percent improvement from baseline using baseline value as 0.1. This is the zero divisor rule.

If patients have a joint injection and/or surgical joint procedure, prior to the date of randomization or during the study, the rules for the joint evaluations will be identical to the joint evaluation rules in Study 5 (see joint evaluation and Table 9.1.11 in Study 5).

Handling of Treatment Failure, Dropouts, and Missing Data for the Improvement in HAQ at Week 24 Primary Endpoint: The following are the missing data imputation rules for **patients who do not meet early escape criteria** at Week 16 in Groups 1, 2, and 3 and all of the patients in Group 4 (irrespective of meeting escape):

1. **If Week 24 HAQ scores are missing,** then the HAQ score at Week 24 will be imputed with last non-missing HAQ score prior to Week 24 (LOCF).
2. **If patients do not have any data through Week 24,** the change from baseline in HAQ at Week 24 will be imputed with the median improvement from baseline in HAQ at Week 24 based on all patients' data.
3. **If baseline HAQ scores are missing,** the baseline HAQ score will be imputed with median HAQ score based on all patients data at baseline.

For patients who **meet early escape criteria** at Week 16 in Groups 1, 2, and 3, the patient's HAQ score at Week 24 will be replaced with HAQ score at Week 16 (scores for patients in Group 4 who meet early escape criteria at Week 16 will not be replaced because they will receive the same treatment during the escape period). The following are the missing data imputation rules for patients who meet early escape criteria at Week 16 in Groups 1, 2, and 3:

1. **If patients do not have any data through Week 16,** the improvement in HAQ at Week 24 will be imputed with the median score of all patient's improvement in HAQ at Week 16.
2. **If Week 16 HAQ scores are missing,** then the HAQ score at Week 24 will be imputed with last non-missing HAQ score prior to Week 16 (LOCF).
3. **If baseline HAQ scores are missing,** the baseline HAQ score will be imputed with median HAQ score based on all subjects' data at baseline.

Methods for the Secondary Efficacy Endpoints: Analyses of the 4 secondary efficacy endpoints will only be considered if positive test results are achieved for the first primary efficacy endpoint (i.e., ACR 20 response at Week 14). There will be four comparisons without any multiplicity adjustments:

1. The combined low and high dose combination groups (i.e., golimumab 50 & MTX and golimumab 100 & MTX, respectively) versus the MTX monotherapy group.
2. The high dose combination group versus MTX monotherapy group.
3. The low dose combination group versus MTX monotherapy group.
4. The golimumab monotherapy group versus MTX monotherapy group.

Methods for the Other Pre-Specified Endpoints: There were no multiplicity adjustments for the 97 pre-specified signs and symptoms endpoints or the numerous other endpoints relating to joint structural damage, physical function, cardiovascular (e.g., cardiovascular adverse reactions, cardiovascular markers), MRI of the wrists and MCPs, the SF-36, the FACIT-F, and the BPI.

Results of the 24-Week Data for Study 6:

Study Dates: December 19, 2005 was the first day a patient enrolled and September 17, 2007 was day the last patient completed the Week 24 period in Study 6.

Patient Disposition: Table 9.2.9 shows the patient disposition through Week 24 in Study 6.

A lower proportion of patients in the combination groups, compared to the golimumab monotherapy and the MTX monotherapy groups, entered early escape. This supports the efficacy of the combination groups in the treatment of the signs and symptoms of RA. A similar proportion of patients in the low and high dose combination groups entered early escape, indicating that there may be no dose response.

A low proportion of patients discontinued the SC study agent, the oral study agent, and the study in all treatment groups. The low dose combination group had the lowest proportion of adverse events leading to discontinuation (DAEs) — see Table 9.2.21.

Table 9.2.9: Patient disposition, n (%), through Week 24 in Study 6

	MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX
Randomized[1]	133 (100%)	133 (100%)	89 (100%)	89 (100%)
Received ≥ 1 dose of SC agent[2]	133 (100%)	133 (100%)	89 (100%)	89 (100%)
Entered the escape phase at W16[3]	42 (31%)	36 (27%)	15 (17%)	14 (16%)
Ended study participation	7 (5.3%)	3 (2.3%)	1 (1.1%)	5 (5.6%)
Discontinued SC study agent through W24	10 (8%)	9 (7%)	2 (2%)	7 (8%)
Adverse event	6 (5%)	7 (5%)	2 (2%)	5 (6%)
Unsatisfactory therapeutic effect	2 (2%)	1 (1%)	0 (0%)	0 (0%)
Lost to follow-up	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Discontinued oral agent administration	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Other	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Discontinued PO agent through W24	10 (8%)	9 (7%)	1 (1%)	7 (8%)
Adverse event	5 (4%)	7 (5%)	1 (1%)	3 (3%)
Discontinued SC agent administration	2 (2%)	1 (1%)	0 (0%)	1 (1%)
Other	1 (1%)	0 (0%)	0 (0%)	2 (2%)
Unsatisfactory therapeutic effect	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Lost to follow-up	1 (1%)	0 (0%)	0 (0%)	1 (1%)

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg) of oral MTX

1 ITT population (patients randomized regardless of whether or not they receive the assigned treatment) was the primary statistical population for the efficacy analyses

2 Treated statistical population (patients who received ≥ 1 dose of SC agent) was the primary statistical population for all the safety analyses and clinical pharmacology analyses. All patients who were randomized were treated with ≥ 1 dose of SC agent

3 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.

Reference: Adapted from Final Study Report for Study 6, Table 3, Page 67; Table 4, Page 70; Disposition Dataset from Study 6

Protocol Deviations: Table 9.2.10 displays the protocol deviations through Week 24 in Study 6. A similar proportion of patients in the treatment groups did not meet eligibility criteria and had a SC and/or oral agent deviation. Most of the patients who did not meet eligibility criteria entered the study and continued study treatment. There was some variability in the receipt of study agent administration including outside the protocol-specified window (within 3-7 days of the study visit).

Table 9.2.10: Protocol deviations in Study 6 through Week 24

	MTX (n=133)	Golimumab100 (n=133)	Golimumab50 & MTX (n=89)	Golimumab100 & MTX (n=89)
Patients who did not meet eligibility criteria	5%	2%	5%	5%
Patients with SC study agent administration deviation	21%	29%	32%	29%
Received administration outside protocol-specified window	20%	26%	30%	26%
Missed an administration	2%	4%	2%	3%
Received an incorrect study agent or incorrect dose	0%	1%	1%	0%
Patients with PO study agent administration deviation	28%	35%	24%	30%
Missed an administration	22%	26%	18%	27%
Received an incorrect study agent or incorrect dose	9%	14%	12%	9%

Reference: Adapted from Final Study Report for Study 6; Attachment 1.10, Page 223; Table 6, Page 76; Attachment 1.15, Page 239.

Baseline Demographics: Table 9.2.11 shows the baseline demographics in Study 6.

The baseline demographic characteristics were similar in all four treatment groups. The demographics were typical of a rheumatoid arthritis population — mostly middle-aged women. The racial demographics in this study are probably a reflection of the countries that participated in this study (e.g., about 15% of the patients in the study were Asian and about 15% of the patients were from Asian countries). In Study 6, about 84% and 16% of the patients lived in non-U.S. and U.S. countries, respectively.

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Table 9.2.11: Baseline demographics in Study 6[1]

		MTX (n=133)	Golimumab100 (n=133)	Golimumab50 & MTX (n=89)	Golimumab100 & MTX (n=89)
Age[2]	Mean (SD)	51 (12) years	50 (11) years	50 (11) years	50 (11) years
Sex	Male	18%	21%	19%	19%
	Female	82%	79%	81%	81%
Race	Caucasian	76%	78%	74%	79%
	Asian	16%	14%	17%	15%
	Other	7%	6%	9%	7%
	Black	2%	2%	0%	0%
Weight	Mean (SD)[2]	73 (19) kg	74 (18) kg	73 (18) kg	70 (16) kg
Height	Mean (SD)[2]	164 (9) cm	164 (10) cm	164 (9) cm	163 (10) cm
Region[3]	Europe, Canada, Australia, & New Zealand	51%	53%	48%	53%
	Asia	16%	14%	16%	15%
	United States	17%	16%	17%	13%
	Latin America and Mexico	17%	17%	19%	19%

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg) of oral MTX
1 All randomized patients (i.e., ITT) were the pre-specified statistical population for the efficacy analyses
2 Mean and medium ages, weights, and heights were similar
3 This reviewer grouped countries into the following regions: European region included European countries (i.e., Germany, Hungary, Poland), Canada, Australia, and New Zealand; Latin America (i.e., Argentina, Chile) and Mexico; Asian countries (i.e., South Korea, Taiwan), and the United States
Reference: Adapted from Final Study Report for Study 6, Table 7, Page 79 and also adapted from the Demographic JMP dataset from Study 6.

Baseline Disease Characteristics: Table 9.2.12 shows the baseline disease characteristics in Study 6.

There were no significant differences in the baseline disease characteristics in the four treatment groups in Study 6 were similar. The four treatment groups had similar disease activity as measured by the DAS28 (CRP) and the ACR core components. In Study 6, 19% of patients had a prior joint injection or procedure, the mean duration of RA disease was 8.3 years, the mean duration of morning stiffness was 2.0 hours, the mean number of swollen joints was 15, and the mean number of tender joints was 26. See Table 6.2 in Section 6.1.2 (Demographics and Baseline Characteristics - RA) for comparisons of the baseline disease characteristics across the 3 RA Phase 3 studies.

Table 9.2.12: Baseline disease characteristics of RA in Study 6[1]

		MTX (n=133)	Golimumab100 (n=133)	Golimumab50 & MTX (n=89)	Golimumab100 & MTX (n=89)
Disease duration, mean (SD)		8.6 (7.9) years	8.3 (7.9) years	7.3 (7.8) years	9.0 (8.3) years
Received MTX in past		100%	100%	100%	100%
Duration of morning stiffness, mean (SD)		1.9 (2.3) hours	1.7 (2.2) hours	2.4 (3.9) hours	2.1 (3.6) hours
Prior joint procedure or injections		34%	31%	31%	33%
Extra-articular manifestations[2]	Rheumatoid nodules	13%	20%	15%	14%
	Sicca syndrome	8%	10%	14%	7%
	Other	2%	3%	6%	2%
	Peripheral neuropathy	1%	1%	1%	2%
	Interstitial lung fibrosis	2%	1%	1%	1%
	Pleuritis	1%	2%	0%	0%
Anatomical stage	Stage I	11%	12%	15%	15%
	Stage II	48%	45%	47%	42%
	Stage III	37%	39%	28%	36%
	Stage IV	5%	5%	10%	8%
Functional class	Class I	13%	14%	9%	12%
	Class II	65%	66%	64%	64%
	Class III	20%	20%	25%	23%
	Class IV	2%	1%	2%	1%
ACR Core Set (median)	# of swollen joints (0-66)	12	11	13	12
	# of tender joints (0-68)	21	22	26	23
	Pain (patient)[3]	5.7	6.0	6.1	6.4
	Disease activity (patient)[3]	5.3	5.6	6.0	5.9
	Disease activity (physician)[3]	5.7	5.8	6.1	6.1
	HAQ disability index (0-3)	1.25	1.38	1.38	1.38
	CRP mg/dL	0.8	0.9	1.0	0.9
# of swollen joints (0-66), mean (SD)		15 (9)	15 (11)	17 (12)	14 (9)
# of tender joints (0-68), mean (SD)		25 (15)	25 (15)	28 (16)	26 (14)
Other Characteristics	DAS28 (CRP) score, median	4.9	4.8	5.1	4.9
	Positive anti-CCP antibodies	81%	80%	81%	76%
	Positive rheumatoid factor	81%	84%	87%	84%

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg) of oral MTX

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

2 Extra-articular manifestations are included only if any group had ≥ 2 manifestations at baseline. No patient in any group had amyloidosis, splenomegaly, or Felty's syndrome at baseline. Only 1 patient in Study 6 had vasculitis, scleritis, or pericarditis at baseline.

3 Assessed on a 0-10 cm VAS

Reference: Adapted from Final Study Report for Study 6; Table 1.18, Page 251-252; Table 8, Pages 82-83; Table 1.19, Pages 253-254

Prior Medications: Table 9.2.13 shows the proportion of patients who received MTX, other DMARDs, immunosuppressives, corticosteroids, and/or NSAIDs prior to enrollment in Study 6.

There were no significant differences in the proportions of patients who received MTX, non- MTX DMARDs, immunosuppressive products, anakinra, steroids, or NSAIDs in the four treatment groups. All patients in Study 6 received MTX in the past which was consistent with the eligibility criteria in Study 6 (e.g., inadequate response to MTX). In Study 6, most patients received a non-MTX DMARD

in the past (i.e., 75%), a significant portion also received an immunosuppressive product in the past (i.e., 14%), the overwhelming majority received systemic steroids in the past (i.e., 88%), and almost all the patients received NSAIDs in the past (i.e., 98%).

Table 9.2.13: Percent of patients who received MTX, other DMARDs, immunosuppressives, corticosteroids, and/or NSAIDs prior to enrollment in Study 6[1]

		MTX (n=133)	Golimumab100 (n=133)	Golimumab50 & MTX (n=89)	Golimumab100 & MTX (n=89)
Received ≥ 1 MTX[2]		**100%**	**100%**	**100%**	**100%**
Prior MTX exposure	**< 1 year**	**25%**	**23%**	**23%**	**19%**
	≥ 1 to < 3 years	**23%**	**31%**	**36%**	**35%**
	≥ 3 years	**51%**	**47%**	**42%**	**45%**
	Unknown	**2%**	**0%**	**0%**	**1%**
Mean (SD) maximum MTX dose within the past 3 months		**17 (3) mg/week**	**17 (3) mg/week**	**17 (3) mg/week**	**17(3) mg/week**
Mean (SD) screening MTX dose		**17 (3) mg/week**	**17 (3) mg/week**	**17 (3) mg/week**	**17(2) mg/week**
Received ≥ 1 non-MTX DMARD		**71%**	**76%**	**79%**	**75%**
Sulfasalazine		**40%**	**41%**	**33%**	**48%**
Hydroxychloroquine		**32%**	**28%**	**43%**	**28%**
Leflunomide		**17%**	**17%**	**20%**	**24%**
Chloroquine		**12%**	**15%**	**17%**	**12%**
Other DMARDs		**8%**	**7%**	**10%**	**6%**
Gold preparations		**12%**	**16%**	**10%**	**18%**
Penicillamine		**4%**	**2%**	**3%**	**5%**
Received ≥ 1 immunosuppressive		**15%**	**10%**	**16%**	**15%**
Cyclosporine		**10%**	**8%**	**10%**	**11%**
Azathioprine		**4%**	**2%**	**3%**	**6%**
Other immunosuppressives		**2%**	**1%**	**5%**	**0%**
Tacrolimus		**0%**	**0%**	**0%**	**0%**
Mycophenolate mofetil		**0%**	**1%**	**0%**	**0%**
Received anakinra		**0%**	**0%**	**1%**	**1%**
Received systemic corticosteroids		**90%**	**85%**	**89%**	**89%**
Received NSAIDs		**97%**	**97%**	**99%**	**98%**

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg) of oral MTX

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

2 Patients must "have been treated with and tolerated MTX at a dose of at least 15 mg/week for at least 3 months prior to screening, and have a MTX dose of ≥ 15 mg/week and ≤ 25 mg/week and stable for at least 4 weeks prior to screening" to have enrolled in Study 6.

Reference: Adapted from Final Study Report for Study 6, Table 1.22, Page 260, Table 1.23, Page 261-265; Table 1.24, Page 266.

Baseline Steroids and/or NSAIDs: Table 9.2.14 displays the proportion of patients who received corticosteroids and/or NSAIDs at baseline in Study 6. Patients were considered to be taking corticosteroids and/or NSAIDs at baseline in Study 6 if it they had been used both prior to **and** after the first study agent administration. The data in Table 9.2.14 differs from the data in Table 9.2.13 which displays the proportion of patients who received treatments for RA prior to enrollment. Also Table 9.2.13 displays the percent of patients who received systemic steroids; whereas, Table 9.2.14 displays the percent of patients who received oral steroids.

There were no significant differences in the use of steroids or NSAIDs at baseline and at Weeks 14 and 24 in the four treatment groups. There were also no significant differences in the use of steroids or NSAIDs at baseline compared to the use of these medications during the trial. Patients remained on stable doses of NSAIDs and steroids during the 24-week controlled portion of Study 6.

Table 9.2.14: Percent of patients who received corticosteroids and/or NSAIDs at baseline, at Week 14, and at Week 24 in Study 6[1]

		MTX (n=133)	Golimumab100 (n=133)	Golimumab50 & MTX (n=89)	Golimumab100 & MTX (n=89)
At baseline	Received oral steroids	65%	68%	75%	70%
	For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	7.0 (3) mg	7.1 (3) mg	6.7 (3) mg	7.0 (3) mg
	Received NSAIDs	86%	83%	87%	84%
At Week 14	Received oral steroids	64%	67%	73%	66%
	For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	7.0 (3) mg	7.4 (6) mg	7.8 (7) mg	6.8 (3) mg
	Received NSAIDs	85%	84%	84%	82%
At Week 24	Received oral steroids	64%	68%	72%	66%
	For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	7.1 (3) mg	7.7 (6) mg	7.7 (7) mg	7.1 (3) mg
	Received NSAIDs	84%	86%	84%	80%

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg) of oral MTX
1 ITT was the pre-specified statistical population for the efficacy analyses (all randomized patients)
Reference: Adapted from Final Study Report for Study 6, Table 10, Page 86 and also adapted from Response to Information Request (Submission #2), Table 2, Page 7.

Results of the major sign and symptom efficacy endpoints in Study 6: Table 9.2.15 displays the results of the major sign and symptoms efficacy endpoints at Weeks 14 and 24 in Study 6. The first primary efficacy endpoint in Study 6 was the proportion of patients with an ACR 20 response at Week 14, using the all-randomized population.

For the primary efficacy endpoint, the high dose combination group, compared to the MTX control group, achieved a greater proportion of ACR 20 responders at Week 14 and the low dose combination group, compared to the MTX control group, achieved a greater proportion of ACR 20 responders at Week 14. These results were statistically significant and support the efficacy of the combination groups for the signs and symptoms of RA.

In addition, the high and low dose combination groups, compared to MTX, achieved a greater proportion of ACR 50 and ACR 70 responders at Week 14. The differential ACR 20, 50, and 70 responses between these treatment groups were maintained at Week 24.

There was no evidence of dose response — the low and high dose combination groups had similar ACR responses at Weeks 14 and 24.

The golimumab monotherapy group had numerically greater proportions of ACR responders compared to the MTX monotherapy group; however, these results were not statistically significant.

All 4 treatment groups had similar baseline DAS28 (CRP) scores. The low and high dose combination groups had lower disease activity, as measured by the DAS28 (CRP), at Week 24 compared to the golimumab and MTX monotherapy groups which supports the efficacy of the combination groups in the treatment of signs and symptoms of RA.

Table 9.2.15: Results of the major sign and symptom endpoints at Weeks 14 and 24 in Study 6

		MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX	Golimumab50 and Golimumab100 & MTX
Randomized patients[1]		133	133	89	89	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[2]	28%	35%	60%	60%	60%
ACR 50 responders	Week 14	10%	20%	35%	29%	32%
	Week 24[2]	14%	20%	37%	33%	35%
ACR 70 responders	Week 14	4%	8%	14%	9%	11%
	Week 24[2]	5%	11%	20%	15%	17%
ACR-N Index, mean (SD)	Week 14	-10 (62)	-4 (78)	23 (46)	19 (51)	21 (48)
	Week 24[2]	-17 (84)	-8 (83)	22 (58)	28 (38)	25 (49)
Patients with W24 DAS28 score		125	125	88	85	173
DAS28 (CRP)[3], mean	Baseline	4.8	4.8	5.0	4.9	5.0
	Week 24	4.1	3.8	3.3	3.0	3.2
	Change	0.7	1.0	1.6	1.9	1.8

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg)

1 The pre-specified statistical population for all ACR responder efficacy analyses in Study 6 were all randomized patients.

2 For the Week 24 analyses, patients in the MTX, golimumab100, and golimumab50 & MTX groups who met early escape criteria at Week 16, each ACR component value at Week 24 was replaced with the corresponding component value at Week 16. Patients in the golimumab100 & MTX group who met early escape criteria at Week 16 continued on their blinded treatment from Week 16 to 24.

3 The DAS 28 (CRP) is an assessment of disease activity and it includes tender joints (0-28), swollen joints (0-28), CRP, and patient's assessment of disease activity. For the DAS28 (CRP) score, there was no missing data imputation. For patients who meet early escape criteria at Week 16 for the MTX, golimumab monotherapy, and the low dose combination group, 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 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 the JMP VISRA dataset in Study 6.

Table 9.2.16 displays the change from baseline in each ACR component at Week 14 in Study 6. The low and high dose combination groups, compared to the MTX and golimumab monotherapy groups had a greater percent improvement in the 7 ACR components.

Table 9.2.16: Change from baseline in each ACR component at Week 14 in Study 6[1]

		Monotherapy Groups		Combination Groups	
		MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX
Number of swollen joints (range is 0-66)	n with measurement	129	129	87	86
	Median # of swollen joints at baseline	12	11	13	12
	Median # of swollen joints at W14	7	6	5	4
	Percent change from baseline at W14	38%	54%	62%	72%
Number of tender joints (range is 0-68)	n with measurement	129	129	87	86
	Median # of tender joints at baseline	21	22	26	23
	Median # of tender joints at W14	14	10	9	10
	Percent change from baseline at W14	30%	49%	60%	60%
Patient's assessment of pain (VAS 0-10 cm)	n with measurement	129	129	87	86
	Median pain at baseline	6	6	6	6
	Median pain at W14	5	4	3	3
	Percent change from baseline at W14	18%	30%	55%	43%
Patient's assessment of disease activity (VAS 0-10 cm)	n with measurement	127	129	87	86
	Median disease activity at baseline	5	6	6	6
	Median disease activity at W14	5	4	3	4
	Percent change from baseline at W14	15%	29%	45%	37%
Physician's assessment of disease activity (VAS 0-10 cm)	n with measurement	129	129	87	86
	Median disease activity at baseline	6	6	6	6
	Median disease activity at W14	4	3	3	3
	Percent change from baseline at W14	35%	40%	55%	54%
HAQ disability index (0-3)	n with measurement	129	129	87	84
	Median HAQ at baseline	1.25	1.38	1.38	1.38
	Median HAQ at W14	1.13	1.13	0.75	0.88
	Percent change from baseline at W14	10%	19%	29%	33%
CRP (mg/dL)	n with measurement	128	129	87	85
	CRP at baseline	0.8	0.9	1.0	0.9
	Median CRP at W14	0.6	0.4	0.3	0.3
	Percent change from baseline at W14	2%	40%	44%	42%

1 These endpoints were included in the 107 pre-specified analyses without multiplicity adjustments.
2 ITT was the pre-specified statistical population (all randomized patients) for the efficacy analyses
Reference: Adapted from Final Study Report for Study 6, Table 3.13, Page 430-432, Table 3.14, Pages 433-435; Table 8, Pages 82-83

The second primary endpoint (change from baseline in HAQ score at Week 24): Table 9.2.17 displays the results of the second primary endpoint in Study 6 (i.e., improvement in HAQ at Week 24).

b(4)

The low and high dose combination groups, compared to the MTX control group, achieved a greater change from baseline in the HAQ at Week 24. The proportion of patients in the low and high dose combination groups, compared to the MTX group, who achieved a minimally clinical important difference (i.e., MCID) was significant [i.e., see Table 6.7 in Section 6.1.5 (Analysis of Physical Function Endpoints – RA) for more details].

Despite the different data handling methods for the improvement in HAQ at Week 24 endpoints in Table 9.2.17 and Table 6.7 in Section 6.1.5 (Analysis of Physical Function Endpoints – RA), the results were similar.

Table 9.2.17: Improvement in HAQ[1] [mean (SD)] at Week 24 (second primary efficacy endpoint) in Study 6[2]

	MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX
n[2]	133	133	89	89
Baseline HAQ score	1.32 (0.7)	1.34 (0.6)	1.41 (0.7)	1.37 (0.7)
Baseline minus Week 24 HAQ score	0.13 (0.6)	0.24 (0.7)	0.47 (0.6)	0.45 (0.5)
p-value (versus MTX)	—	0.240	< 0.001	< 0.001

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks; MTX is the background weekly oral MTX used prior to enrollment (15-25 mg) of oral MTX

1 Improvement in HAQ at Week 24 is the baseline HAQ score minus the Week 24 HAQ score (positive values indicate less disability and negative values indicate more disability). HAQ score is from 0 (best score) to 3 (worst score).

2 ITT was the pre-specified statistical population (all randomized patients) for all of the efficacy analyses including the co-primary endpoints

Reference: Adapted from Final Study Report for Study 6, Table 14, Page 109; Table 8, Page 83

Subgroup Efficacy Analyses: Table 9.2.18 presents subgroup efficacy analyses in Study 6 of the MTX monotherapy control group compared to the combined low and high dose combination groups, using the primary efficacy endpoint, by demographics. Table 9.2.19 presents the subgroup efficacy analyses in Study 6 of the MTX monotherapy control group compared to the combined low and high dose combination groups, using the primary efficacy endpoint, by disease duration, RF status, and baseline medication use. In these subgroup analyses, the combined low and high dose combination groups instead of the individual low and high dose combination groups to increase the sample size and because there was no evidence of a dose response between the low and high dose combination groups.

There was no clear evidence of a differential response between the combined combination groups compared to the MTX group in the proportion of ACR 50 responders at Week 24 in the demographic subgroups evaluating gender, race, age, and weight. In the geographic subgroup, the Latin American subgroup had a poorer response in the compared to patients in the other regions. However, since this subgroup was small and in Study 5, patients from Latin America had a greater response than patients from other regions, no conclusions can be drawn about the response in patients from Latin America compared to patients from the other regions.

There was no clear evidence of a differential response between the combined combination groups compared to the MTX group in the proportion of ACR 50 responders at Week 24 in the disease duration, RF status, and baseline medication use subgroups.

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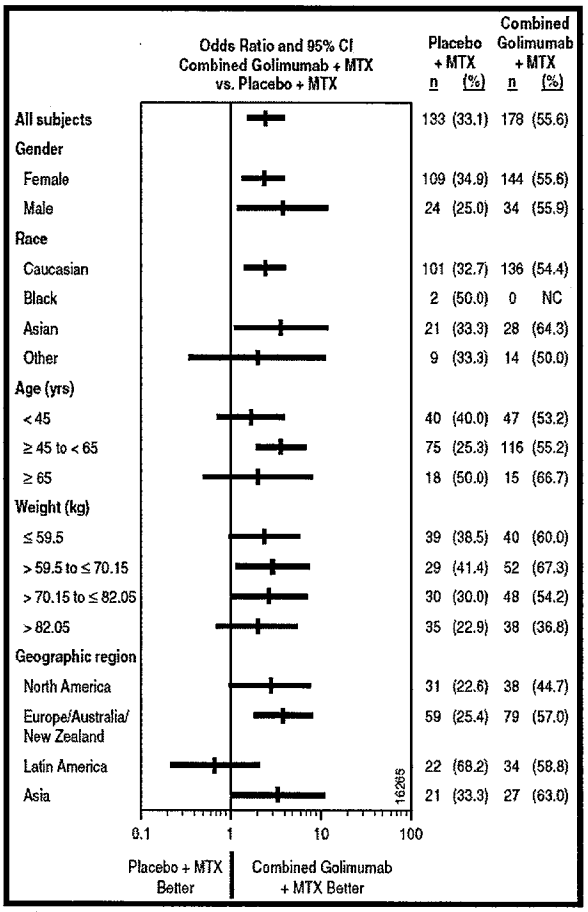
Figure 9.2.18: Efficacy (i.e., ACR 20 responders at Week 14) of the combined golimumab combination groups[1] vs. the MTX monotherapy group by demographic subgroups in Study 6[2]

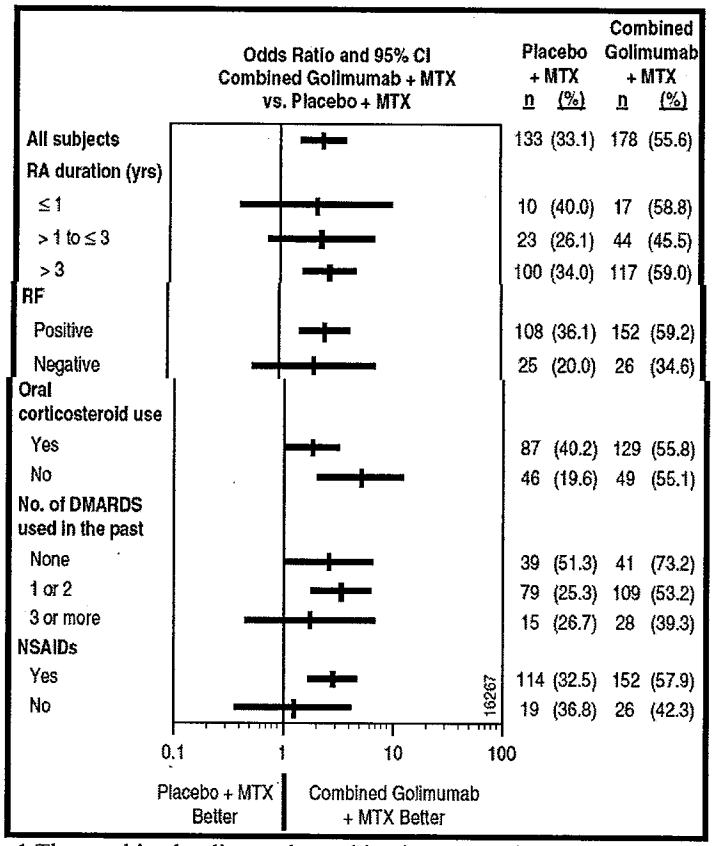


1 The combined golimumab combination groups include the golimumab50 & MTX group and the golimumab100 & MTX group. The combination groups do not include the golimumab100 monotherapy group. Centocor only seeks approval for the combination of golimumab and MTX for the signs and symptoms of RA; Centocor does not seek approval for the golimumab monotherapy group.

2 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 Week 14 and p is the proportion of patients in the placebo group with an ACR 20 response at Week 14. 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 ACR 20 response at Week 14 was the primary efficacy analysis for Study 6.

Reference: Adapted from the final study report for Study 6, Attachment 3.55, Page 525

Figure 9.2.19: Efficacy (i.e., ACR 20 responders at Week 14) of the combined golimumab combination groups[1] vs. the MTX monotherapy group by disease duration, RF status, and baseline medication use in Study 6[2]



1 The combined golimumab combination groups include the golimumab50 & MTX group and the golimumab100 & MTX group. The combination groups do not include the golimumab100 monotherapy group. Centocor only seeks approval for the combination of golimumab and MTX for the signs and symptoms of RA; Centocor does not seek approval for the golimumab monotherapy group.

2 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 Week 14 and p is the proportion of patients in the placebo group with an ACR 20 response at Week 14. 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 ACR 20 response at Week 14 was the primary efficacy analysis for Study 6.

Reference: Adapted from the final study report for Study 6, Attachment 3.56, Page 526; Attachment 3.57, Page 527

Exposure: Table 9.2.20 displays the golimumab and MTX exposure through Week 24 in Study 6.