Table 7.7.1: Safety, immunogenicity, and bioequivalence results in Study 24

		LIV	PFS
Treated patients		79	77
Average duration of follow-up		10 weeks	10 weeks
Safety	AEs, %	49%	36%
	Infections, %	2.5%	0%
	Injection site reactions, %	0%	0%
Immunogenicity	Positive HAHA, n (%)	1 (1%)	1 (1%)
Bioequivalence Results	Cmax (µg/mL), geometric mean	5.9	6.5
	Ratio of geometric means of Cmax (90% CI)	—	110.7 (96.1,127.4)
	AUC (µg•day/mL), geometric mean	88.9	95.2
	Ratio of geometric means of AUC (90% CI)	—	107.1 (95.2, 120.6)

Reference: Adapted from Study 24, Attachment 3.1 Pages 266-268; Table 6, Page 52

Table 7.7.2 presents safety and immunogenicity of the LIV and PFS presentations in the long-term extension portions of Studies 8, 9, and 11. The safety and immunogenicity data of the PFS presentation from Studies 5 and 6 is limited and therefore not presented in Table 7.7.2.

In the long-term extensions of Studies 8, 9, and 11, 1.7% of patients who continue to receive LIV and 1.2% of patients who were switched to PFS had positive antibody to golimumab conversions.

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 by AUC.

Table 7.7.2: Safety and immunogenicity of the LIV and PFS presentations in the long-term extension portions of Studies 8, 9, and 11 (Week 24 through the safety cut-off)[1]

Presentation	LIV	PFS	
		1 or 2 doses	≥3 doses
Patients treated with golimumab in the long-term extensions of Studies 8, 9, & 11	797	168	943
Patients with appropriate antibody samples	733	129	399
Patients with HAHA	3.4%	1.6%	1.8%
Injection-site reactions in the patients with HAHA	3.4%	0%	0%
Anaphylactic or serum sickness reactions	0%	0%	0%
Serious or severe injection site reactions[2]	0%	0%	0%

1 The PFS safety cut-off date was March 14, 2008.
2 There were no serious or severe injection site reactions of the LIV and PFS presentations in the long-term extensions of Studies 8, 9, and 11. There was only one severe injection site reaction after LIV use in the controlled portions of the 5 Phase 3 trials.
Reference: Adapted from 120-Day Safety Update, Table 18, Page 106; Appendix A.70, Pages 463-466; Table 19, Page 107

7.7.2 Safety in Asthma Trial

Golimumab was evaluated in a one-year, randomized, double-blind, placebo-controlled, Phase 2 trial in patients with severe persistent asthma who were symptomatic despite inhaler steroids and long-acting beta$_2$-agonists (Study 3). Study 3 was terminated early by Centocor because golimumab did not demonstrate efficacy in the co-primary efficacy endpoints (change from baseline in FEV1 at Week 24 and the number of severe asthma exacerbations through Week 24) or the major secondary endpoints and because of the golimumab-associated toxicities (e.g., serious infections, malignancies).

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This section will explore the golimumab-associated toxicities in the asthma trial and evaluate the implications of these toxicities for the rheumatology populations.

Table 7.7.3 presents the major safety results from the asthma trial (Study 3) including deaths, SAEs, DAEs, AEs infections, and malignancies through Week 76. Because the trial was terminated early, the mean duration of **follow-up** for the golimumab and the placebo groups was 60 and 68 weeks, respectively. The mean **exposure** of golimumab and the placebo groups was 44 and 51 weeks, respectively (exposure was considered to be 4 weeks after the last administration of study agent). Therefore, the time period for the safety results in Table 7.7.3 may include several weeks after dosing in which there was no exposure to the study agent.

A greater proportion of patients in all the golimumab groups, compared to the placebo group, had SAEs, DAEs, infections that required oral or parental antibiotics, and serious infections. There was no clear dose-relationship to these particular AEs. A greater proportion of patients in all the golimumab groups had malignancies, compared to the placebo group. Higher golimumab doses had a greater proportion of malignancies than lower doses suggesting a possible dose-relationship.

Table 7.7.3: Deaths, SAEs, DAEs, AEs, and AEs of special interest (e.g., infections, malignancies) in the asthma trial (Study 3) through Week 76[1]

	Placebo	Golimumab50[2]	Golimumab100[2]	Golimumab200[2]
Treated patients	78	77	76	78
Deaths[3], n (%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
SAEs, %	21%	32%	31%	28%
DAEs, %	5%	18%	18%	14%
AEs, %	96%	92%	99%	100%
Infections				
Infection AEs, %	69%	67%	71%	72%
Infections that Required Oral or Parental Antimicrobial Treatment, %	58%	61%	64%	62%
Serious Infections, %	9%	19%	15%	13%
Malignancies				
All Malignancies, n (%)	0 (0%)	1 (1%)	2 (3%)	5 (6%)
Malignancies except NMSC, n (%)	0 (0%)	1 (1%)	2 (3%)	3 (4%)
NMSC, n (%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)

1 All of the AEs included in this table (except for DAEs) occurred through Week 76 (20 weeks after the last exposure to golimumab assuming that exposure to golimumab is 4 weeks after the last dose). The mean exposure of golimumab and the placebo groups to the study agent was 44 and 51 weeks, respectively (exposure was considered to be 4 weeks after the last administration of study agent). However, the mean duration of follow-up for the golimumab and the placebo groups was 60 and 68 weeks, respectively. The DAEs were through Week 52.

2 The starting dose of the golimumab50 group was 75 mg at Week 0 then 50 mg every 4 weeks from Weeks 4 to 52, the starting dose of the golimumab100 group was 150 mg at Week 0 then 100 mg every 4 weeks from Weeks 4 to 52, and the starting dose of the golimumab200 group was 300 mg at Week 0 then 50 mg every 4 weeks from Weeks 4 to 52.

3 One patient in the golimumab200 group died of septic shock (see the narrative in Section for more details).

Reference: Final study report for Study 3; Table 3, Page 53; Attachment 4.10, Page 451; Attachment 4.20, Page 514; Attachment 4.17, Page 498; Attachment 4.18, Page 506; Attachment 4.8, Page 446; Attachment 4.4, Page 403

Table 7.7.4 presents the exposure-adjusted serious infections in the asthma trial and compares the observed exposure-adjusted malignancies in the asthma trial to the expected rate of malignancies in the general U.S. population based on the SEER database. Note Table 7.7.4 is based on patient-years of follow-up through Week 76 rather than patient-years of exposure. Both analyses would likely produce the same qualitative results.

The incidence of serious infections per 100-patient years in the golimumab groups, compared to the placebo groups, was higher. The number of malignancies other than NMSC was greater in the golimumab groups than expected compared to the general U.S. population and the number of malignancies other than NMSC in the placebo group was lower than expected compared to the general U.S. population.

Table 7.7.4: Serious infections and observed and expected malignancies in the asthma trial according to the SEER database[1]

	placebo	golimumab
Patients treated	79	231
Patient-years of follow-up	102	261
Serious Infections		
Serious infection, n (%)	7 (9%)	36 (16%)
Incidence of serious infections per 100 patient-years (95% CI)	10.8 (5.4, 19.3)	21.4 (16.2, 27.8)
Malignancies except NMSC		
Malignancies except NMSC, n	0	6
Incidence of malignancies except NMSC per 100 patient-years	0	2.3
Expected # of patients with ≥ 1 (SEER)[1]	0.6	1.7
SIR (95% CI)[2]	0 (0,4.7)	3.5 (1.3, 7.5)

1 Based on the SEER database from 2004, adjusted for age, gender, and race.
2 SIR is the standardized incidence ratio (**observed** number of patients with malignancy **divided by** the **expected** number of patients with malignancy).
Adapted from the 120-Safety Update Report, Appendix A.26, Page 368, Appendix A.32, Pages 381-3; Appendix A.33, Pages 384-385.

Table 7.7.5 displays the type of malignancies in Study 3.

Table 7.7.5: Malignancies in Study 3

Dose[2]	n	Patient#	Type of Cancer
200 mg	78	1. 0303-003	Colon adenocarcinoma stage 0
		2. 0501-007	Metastatic renal cell adenocarcinoma
		3. 1001-002	Epithelial cervical CA
		4. 1400-015	Basal cell skin CA
		5. 1424-004	Basal cell skin CA
100 mg	78	6. 1441-013	Metastatic melanoma
		7. 0705-016	B-cell follicular lymphoma
50 mg	75	8. 1002-016	Invasive tubular breast CA
Placebo	78	N/A	none

Reference: Final study report for Study 3; Attachment 4.15, Pages 490-492

It is important to evaluate why a malignancy signal was seen in the asthma trial and not the larger safety database for the rheumatology Phase 3 trials. Table 7.7.6 presents demographics, history of smoking, family history of malignancy, and oral steroid use in the asthma trial compared to the 5 Phase 3 trials of RA, PsA, and AS. Although Table 7.7.6 includes some important risk factors for cancer including age, smoking history, and family history of cancer, this table is not a complete evaluation of the risks for cancer in these trials.

Patients were not allowed to enroll in the asthma trial if they had a significant smoking history — patients had to have less than a 10 pack year smoking history and had to be a nonsmoker for at least one year. A smaller percentage of patients in the asthma trial had a smoking history compared to the

patients in the rheumatology trials. Therefore, smoking history cannot explain the differential relative occurrence of malignancy in the asthma trial.

The demographics in the asthma trial were similar to one or more of the rheumatologic populations, which in fact reflects a middle-aged demographic rather than the younger ages that one typically considers as purely asthmatic. The patients also were, on average, treated with higher doses of steroids, which are also immunosuppressive. It is not clear if any of these factors contributed to the differential relative occurrence of malignancy in the asthma trial.

One possible explanation for the differential risk of malignancies in the asthma trial was that the asthma trial included a higher dose (200 mg) that was not used in the rheumatologic trials. Assuming this were true, approval of the lowest effective golimumab dose (50 mg) would be prudent.

The data overall do not permit definite conclusions regarding the differential risk of malignancies in the asthma and rheumatologic populations.

Table 7.7.6: Comparative demographics, history of smoking, family history of malignancy, and oral steroid use in the asthma trial and the 5 Phase 3 RA, PsA, and AS trials

	Asthma Trial	Rheumatology Trials		
		3 RA Phase 3 Trials	PsA Trial	AS Trial
Treated patients	309	1537	405	355
Age, mean	50 years	51 years	47 years	39 years
History of smoking, %[2]	26%	41%	44%	57%
Smoking at baseline, %[2]	N/A[2]	19%	18%	36%
Family History of Malignancy, %	N/A	29%	24%	30%
Female, %	56%	81%	40%	28%
Caucasian, %	88%	78%	97%	74%
Black, %	11%	3%	0%	1%
Asian, %	1%	12%	2%	24%
Europe, Australia, Canada, & New Zealand	57%	46%	78%	53%
Latin America & Mexico	0%	13%	0%	0%
United States, %	43%	29%	24%	24%
Asia, %	0%	12%	0%	23%
Weight, mean	184 pounds	164 pounds	187 pounds	171 pounds
Received any oral corticosteroid, %[3]	52%	57%	17%	16%
For patients who received oral steroids, mean daily dose of corticosteroid (mg of prednisone equivalent)[3]	13.4 mg	7 mg	7 mg	6 mg

1 The starting dose of the golimumab50 group was 75 mg at Week 0 then 50 mg every 4 weeks from Weeks 4 to 52, the starting dose of the golimumab100 group was 150 mg at Week 0 then 100 mg every 4 weeks from Weeks 4 to 52, and the starting dose of the golimumab200 group was 300 mg at Week 0 then 50 mg every 4 weeks from Weeks 4 to 52.

2 The eligibility criteria in the asthma trial stated that patients had to have less than a 10 pack year history of smoking and must not have smoked in the year prior to entering the trial. Patients were excluded if they had a history of COPD or other significant respiratory disorder.

3 For the asthma trial, the proportion of patients who used steroids and the mean daily dose of corticosteroid for the asthma trial were from randomization through Week 24. In contrast, the proportion of patients who used steroids and the mean daily dose of corticosteroids for the rheumatology Phase 3 trials were at baseline. However, the proportion of patients who used steroids and the mean daily dose of corticosteroids through Week 24 in the Phase 3 trials was very similar to the baseline values.

Reference: Final study report for Study 3; Table 5, Page 58; Attachment 1.20, Page 186; JMP demographic datasets in Study 3 and JMP datasets for the 5 Phase 3 trials; Final Study Report for Study 8, Attachment 1.13; Final Study Report for Study 9, Attachment 1.14, Final Study Report for Study 5, Attachment 1.16; Final Study Report for Study 6, Attachment 1.21; Final Study Report for Study 11, Attachment 1.14

7.7.3 Human Reproduction and Pregnancy Data

No studies of golimumab were conducted in pregnant or lactating women. Centocor proposes that golimumab be the same pregnancy class as the 4 approved TNF inhibitors (Pregnancy Category B).

In the 13 submitted golimumab studies, there were 11 pregnancies in patients who received study medication (see Table 7.7.7) and 10 pregnancies in partners of patients who received study medication (see Table 7.7.8) as of the last safety cut-off. Pregnancies occurred in the Studies 3, 5, 8, 9, 11, and 24. No pregnancies occurred in Studies 466-1, 466-2, 1, 2, 6, 13, and 23.

Very few patients became pregnant in the golimumab studies, which is consistent with study mandated requirements regarding contraception. Because so few patients have become pregnant, the data are not definitive with respect to possible treatment-related effects of golimumab on pregnancy, but the number of miscarriages and spontaneous abortions does not appear to be excessively elevated, particularly in the setting of older patients with multiple comorbidities and medications. Most of the females who were pregnant were in the RA studies and were likely also on MTX, which is a known teratogen. Despite this, no congenital anomalies have been observed thus far.

Table 7.7.7: Outcomes of 11 pregnancies in female patients who received study medication in one of the 14 submitted golimumab studies in the BLA[1]

	Treatment	Study	Patient	Outcome
1	golimumab200	3	1400-030	Miscarriage
2	golimumab100	3	0704-012	Spontaneous abortion
3	golimumab100	5	7433-50537	Spontaneous abortion
4	golimumab100	5	7414-50066	Pregnancy ongoing
5	golimumab50	11	7431-10189	Pregnancy ongoing
6	placebo to golimumab50	5	7409-50015	Pregnancy ongoing
7	placebo to golimumab50	8	2017-80065	Spontaneous abortion
8	placebo to golimumab50	9	7439-90104	Pregnancy ongoing
9	placebo to golimumab50	11	2019-10395	Pregnancy ongoing
10	placebo	11	7404-10156	Delivered a healthy baby
11	placebo	11	3014-10590	Elective abortion

1 Through the last safety cut-off date of January 31, 2008 from the Summary of Clinical Safety Reference: Adapted from the SCS, Table 20, Pages 175-176.

Table 7.7.8: Outcomes of 10 pregnancies in partner's of male patients who received study medication in one of the 14 submitted golimumab studies in the BLA[1]

	Treatment	Study	Patient	Outcome
1	golimumab200	3	0902-008	No information – withdrawal of consent
2	golimumab100	5	1007-50707	Partner delivered a healthy female infant
3	golimumab100	9	7439-90085	Status unknown
4	golimumab100	24	001-184	Partner had a spontaneous abortion
5	golimumab50	9	3001-90119	Partner delivered a healthy female infant
6	placebo to golimumab50	8	5209-80397	Partner delivered a healthy female infant
7	placebo to golimumab50	8	7410-80437	Partner delivered a mature female infant had hypoglycemia due to the mother's insulin
8	placebo to golimumab50	8	2018-80463	Partner's pregnancy ongoing
9	placebo to golimumab50	9	2010-90091	Status unknown
10	placebo to golimumab50	9	2001-90141	Status unknown

1 Through the last safety cut-off date of January 31, 2008 from the Summary of Clinical Safety Reference: Adapted from the SCS, Table 20, Pages 175-176.

7.7.4 Pediatrics and Effect on Growth

In this BLA, Centocor did not submit any studies of golimumab in pediatric patients. Centocor has not yet begun any studies of golimumab in pediatric patients. See section 1.4 for a discussion of Centocor's proposals for addressing PREA requirements.

7.7.5 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no occurrences of overdose during any of the 13 submitted golimumab studies.

The highest golimumab dose was administered in Study 466-1 (a randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study of IV golimumab in patients with active RA). In Study 466-1, 5 patients with RA received single doses of 10 mg/kg of IV golimumab and these patients did not experience SAEs or other significant reaction. Since these 5 patients had a mean weight of 77 kg, the mean IV golimumab dose was 770 mg and since the heaviest patient weighed 100 kg the highest IV golimumab administered was 1000 mg.

TNF inhibitors are not known to have abuse potential so no abuse potential studies of golimumab were performed.

7.8 Additional Submissions

Table 7.8.1 displays additional safety submissions to this BLA. All of the safety information in these submissions has been incorporated into this review. Submissions relating to CMC, compliance, pharmacology/toxicology, and CDRH's review of the autoinjector are not included in Table 7.8.1.

Table 7.8.1: Additional clinical safety submissions

Type of Submission	Date of Centocor Submission (sequence #)	Date of DAARP IR	Comments
Original BLA Submission[1]	**6/24/08 (#0)**	**N/A**	**–**
Response to an IR	**10/3/08 (#2)**	**9/5/08**	**1. Corticosteroid and NSAID use at Weeks 14 and 24 during the Phase 3 trials** **2. Intension and rationale on continuing the use of the 100 mg in the long-term extensions**
120-day Safety Update[2]	**10/21/08 (#5)**	**N/A**	**–**
Response to an IR	**10/31/08 (#7)**	**9/5/08**	**Pediatric Development Plan**
Response to an IR	**12/19/08 (#13)**	**10/8/08**	**Proposed REMS and Revised Label**

IR is information request

1 The safety cut-off dates for the original submission was in September 2008 (September 5th, 5th, 19th, 26th, and 27th for Studies 8, 9, 6, 11, and 5, respectively). However, the safety cut-off date for all SAEs and deaths was January 31, 2008 and April 15, 2008, respectively.

2 The safety update includes updated analyses of safety data in the golimumab clinical trials through June 2, 2008 with deaths reported through July 31, 2008 (representing up to 8 months of additional golimumab exposure).

8 Postmarketing Experience

There is no post-marketing experience for golimumab because golimumab is not approved in any country.

9 Appendices

9.1 Literature Review/References

Dixon, WG et al. "Serious Infection Following Anti–Tumor Necrosis Factorα Therapy in Patients With Rheumatoid Arthritis." *Arthritis & Rheumatism* 2007;56(9): 2896-2904.

Gonzalez, Angel et al. "The Widening Mortality Gap Between Rheumatoid Arthritis Patients and the General Population." *Arthritis & Rheumatism* 2007;56(11): 3583-3587.

Listings, Joachim et al. "Infections in Patients With Rheumatoid Arthritis Treated With Biologic Agents." *Arthritis & Rheumatism* 2005;52(11): 3403-3412.

Saag, Kenneth et al. "American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis." *Arthritis & Rheumatism* 2008;59(6): 762-784.

Schwabe, Robert and Brenner, David. "Mechanisms of Liver Injury: TNF-α-induced liver injury: role of IKK, JNK, and ROS pathways." *Am J Physiol Gastrointest Liver Physiol* 2006;290: G583–G589.

Wolfe F, and K Michaud. "Biologic Treatment of Rheumatoid Arthritis and the Risk of Malignancy." *Arthritis & Rheumatism* 2007;56(9): 2886-2895.

9.2 Labeling Recommendations

The following are the major changes recommended for Centocor's proposed labeling for golimumab. These recommendations may change after internal labeling discussions and after labeling discussions with Centocor.

INDICATIONS AND USAGE:

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1 Page(s) Withheld

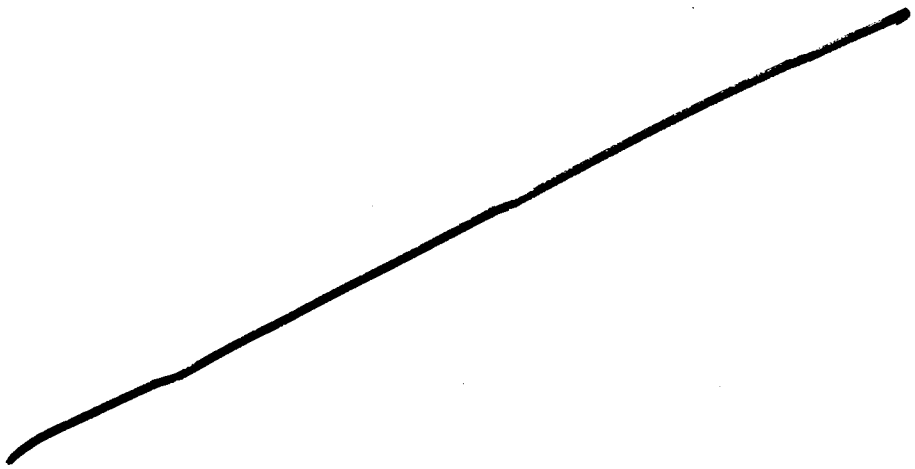
_____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Medical-*1



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9.3 Advisory Committee Meeting

No Advisory Committee Meeting was requested by the FDA because golimumab would be the fifth approved TNF inhibitor in the United States (the fourth approved TNF inhibitor for the treatment of the signs and symptoms of RA, PsA, and AS); the safety profiles of TNF inhibitors are well-established; the efficacy and safety of golimumab appeared similar to the efficacy and safety of the other TNF inhibitors in the treatment of the signs and symptoms of RA, PsA, and AS; and there were no unexpected safety signals detected in the golimumab BLA.

9.4 Individual Study Reports

9.4.1 Study C0524T05 (Study 5) – RA (MTX-naive)

The following description of the protocol for Study C0524T05 (Study 5; GO-BEFORE) is based on amendment 3 of the protocol (dated March 22, 2007) and amendment 1 of the SAP (dated April 9, 2007). See Table 9.1.1 for the dates of all amendments to the protocol and SAP for Study 5.

In Study 5, the first patient consented on December 12, 2005 and the last patient completed Week 24 on October 1, 2007. The final protocol amendment (amendment 3) and the final SAP (amendment 1) occurred prior to the 24-week database lock in Study 5. In amendment 3 of the protocol, there were no significant changes to the study conduct of Study 5 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 9.1.1: Amendments to the Study 5 protocol and SAP

	Amendment	Date
Protocol	Original Protocol	August 25, 2005
	Amendment 1 to Protocol	November 11, 2005
	Amendment 2 to Protocol	February 8, 2007
	Amendment 3 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 October 1, 2007 or after this date.
1 Amendment 3 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 for Study 5

Title: Study C0524T05 (Study 5; GO-BEFORE) is entitled, "A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in Methotrexate-naïve Subjects with Active Rheumatoid Arthritis."

Objectives of Study 5: The primary objectives of this study were to assess the efficacy of golimumab (i.e., reduction of the signs and symptoms at Week 24 and inhibition of progression of structural damage at Week 52) in patients with active RA who have not been previously treated with MTX.

The secondary objectives were to assess the safety of golimumab, the effect of golimumab on physical function and quality of life, the pharmacodynamics, and pharmacokinetics of golimumab in patients with active RA who have not been previously treated with MTX.

Overall Design of Study 5: Ongoing, 5-year, randomized, double-blind (DB), MTX-controlled, multi-center, global, 4-arm, Phase 3 trial of SC golimumab in patients with active RA who were MTX-naive (i.e., have not received more than 3 weekly doses of MTX for RA at any time) and had never received a TNF inhibitor, rituximab, natalizumab, or a cytotoxic agent. Patients may have taken stable doses of NSAIDs and corticosteroids equivalent to ≤ 10 mg prednisone/day. The use of DMARDs or

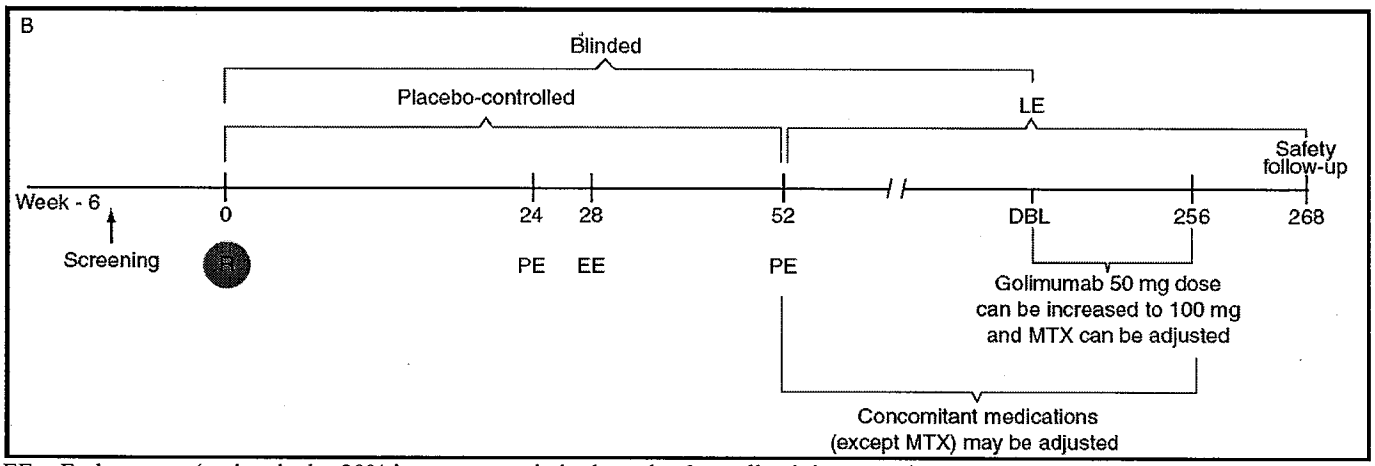
systemic immunosuppressive products (other than the study agents) was prohibited through Week 52 of the study and the use of other biologic agents, cytotoxic agents, and investigational agents was prohibited during the entire 5-year study. The treatment period consisted of the following 2 main periods (see Figure 9.1.2 for the schema of Study 5):

1. Double-Blind (DB), Controlled Period: 52-week DB, MTX-controlled period with two parts:

   - 28-week period from Week 0 to Week 28
   - 24-week period from Week 28 to Week 52 (where at Week 28 patients could have entered into an escape phase for lack of efficacy)

2. Long-term Extension (LE) Period: 4-year, LE Period from Week 52 to until Week 256. The initial part of the LE Period was be DB but the time period after the Week 52 database lock was open-label (the Week 52 database lock occurred when the last patient completed the one-year controlled portion of the study).

Figure 9.1.2: Study 5 schema



EE = Early escape (patient had < 20% improvement in both tender & swollen joint counts)
PE = Primary endpoint (Initial primary endpoint was ACR50 response at Week 24 and second primary endpoint was structural progression at Week 52)
DBL = 52-week database lock (i.e., after last patient completes Week 52 visit)
LE = Long-term extension (the last golimumab dose during the LE was at Week 252 – exposure will be up until 256). Safety follow-up in the LE was up to Week 268 (about 12 weeks without exposure to golimumab).
R = randomization
Placebo-controlled refers to the MTX only treatment group
Four Database locks occurred at Weeks 24, 52, 104, and 268 after all patient evaluations.
Reference: Adapted from amendment 3 of Protocol 5, Figure 1, Page 20.

Eligibility Criteria of Study 5: Table 9.1.3 displays the eligibility criteria in Study 5.

Table 9.1.3: Eligibility Criteria in Study 5

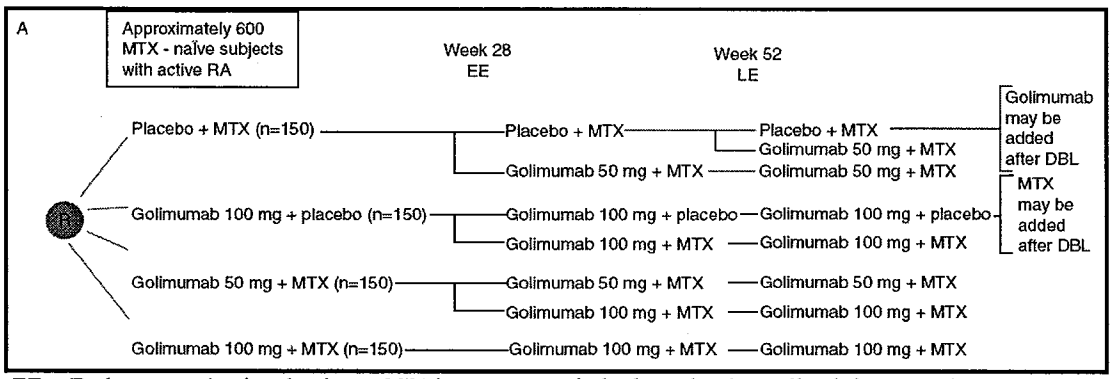
Inclusion Criteria: To have been eligible to participate in the study, patients had to have met all of the following criteria:	**Exclusion Criteria:** If patients had any of the following conditions, they were not eligible to participate in the study:
1. ≥ 18 years old and diagnosed with RA (for at least 3 months prior to first administration of study drug), according to the revised 1987 criteria of the American Rheumatism Association. 2. Had active RA defined by persistent disease activity with at least 4 swollen and 4 tender joints, at the time of screening and baseline, and at least 2 of the following 4 criteria: 2.1. CRP ≥ 1.5 mg/dL at screening or ESR by Westergren method of ≥ 28 mm in the first hour at screening or baseline. 2.2. Morning stiffness of ≥ 30 minutes at screening and baseline. 2.3. Bone erosion by x-ray and/or MRI prior to first administration of study drug. 2.4. Anti-cyclic citrullinated peptide (anti-CCP) antibody-positive or RF-positive at screening. 3. MTX-naïve (i.e., have not received more than 3 weekly doses of MTX for RA at any time). 4. If used oral corticosteroids, must have been on a stable dose equivalent to ≤ 10 mg of prednisone/day for at least 2 weeks prior to first administration of study agent. If did not use corticosteroids, must not have received oral corticosteroids for at least 2 weeks prior to first administration of study agent. 5. If used NSAIDs or other analgesics for RA, must have been on a stable dose for at least 2 weeks prior to the first administration of study agent. 6. Considered eligible according to the following TB screening criteria: 6.1 No history of latent or active TB prior to screening. 6.2 No signs or symptoms suggestive of active TB upon medical history and/or physical examination. 6.3 No recent close contact with a person with active TB or, if there was such contact, was referred to a physician specializing in TB to undergo additional evaluation and, if warranted, received appropriate treatment for latent TB prior to or simultaneously with the first administration of study drug. 6.4. Within 6 weeks prior to the first administration of study agent, either had negative diagnostic TB test results (defined as both a negative tuberculin skin test and a negative QuantiFERON-TB Gold test), or had a newly identified positive diagnostic TB test result (defined as either a positive tuberculin skin test or a positive QuantiFERON-TB Gold test) during screening in which active TB has been ruled out and for which appropriate treatment for latent TB was initiated either prior to or simultaneously with the first	1. Inflammatory diseases other than RA that might confound the evaluation of the benefit of golimumab (e.g., PsA, AS, systemic lupus erythematosus, or Lyme disease). 2. Received infliximab, etanercept, adalimumab, rituximab, natalizumab, or a cytotoxic agent (e.g., including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents). 3. Within the 4 weeks prior to the first administration of study agent, received DMARDs/systemic immunosuppressives (e.g., leflunomide, D-penicillamine, hydroxychloroquine, chloroquine, oral or parenteral gold, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil, anakinra, or intra-articular, IM, or IV corticosteroids, including adrenocorticotropic hormone). 4. Within 3 months prior to the first administration of the study agent received alefacept or efalizumab. 5. Received any investigational agent within 5 half-lives prior to the first administration of study agent. 6. History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection (e.g., recurrent pyelonephritis, chronic nonremitting cystitis), an open, draining, or infected skin wound, or an ulcer. History of an infected joint prosthesis, or received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced. 7. Known to be infected with HIV, hepatitis B, or hepatitis C. 8. Had a serious infection (e.g., hepatitis, pneumonia, pyelonephritis, or sepsis) or have been hospitalized for an infection or within 2 months prior to administration of study agent treated with IV antibiotics for an infection. Although, less serious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) were not exclusionary. 9. History of active or latent granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis. 10. Within 6 months prior to screening had a nontuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, Pneumocystis carinii, aspergillosis). 11. Received, or was expected to receive during the trial (within 3 months before the first administration of study agent or within 6 months after the last administration of study agent) any live virus or bacterial vaccination. 12. History of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease (e.g., lymphadenopathy of unusual size or location, or clinically significant splenomegaly). 13. Known malignancy with the exception of a nonmelanoma skin cancer that was treated with no evidence of recurrence. 14. Had a transplanted organ (with the exception of a corneal transplant performed > 3 months prior to first study agent

administration of study drug. 6.5. Had posterior-anterior and lateral chest radiographs, taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB. 7. Screening laboratory test results: 7.1 Hemoglobin $\geq$ 8.5 g/dL. 7.2 White blood cells $\geq 3.5 \times 10^9$ cells/L. 7.3 Neutrophils $\geq 1.5 \times 10^9$ cells/L. 7.4 Platelets $\geq 100 \times 10^9$ cells/L. 7.5 ALT and AST levels not exceeding 1.5 times the ULN. 7.6 Creatinine not exceeding 1.5 mg/dL. 8. Women of childbearing potential (WOCP) or men capable of fathering children must have been using adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization) during the study and for 6 months after receiving the last administration of study drug. WOCP must test negative for pregnancy. 9. Was willing and able to adhere to the study visit schedule and other protocol requirements and was capable of providing informed consent, which must have been obtained prior to any study-related procedures.	administration). 15. Had a chest radiograph within 3 months prior to the first administration of study agent that showed an abnormality suggestive of a malignancy or current active infection, including TB. 16. Had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening. 17. History of known demyelinating disease such as multiple sclerosis or optic neuritis. 18. History of, or concurrent, CHF, including medically controlled, asymptomatic CHF. 19. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease. 20. Known hypersensitivity to human immunoglobulin proteins or other components of golimumab. 21. Had a substance abuse (drug or alcohol) problem within the previous 3 years. 22. Unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy access. 23. Was participating in another trial with an investigational agent or procedure. 24. Pregnant, nursing, or planning a pregnancy or fathering a child within 6 months after receiving the last administration of study agent.

Reference: Adapted from amendment 3 of Protocol 5, pages 24-28

Treatments in Study 5: Patients received study treatment during the DB and LE Periods (see Figure 9.1.4). Golimumab was supplied as a sterile liquid (i.e., liquid in a vial or LIV) for SC injection during the DB Period and was supplied as LIV or a sterile liquid for SC injection in prefilled syringe (PFS) in the LE Period.

Figure 9.1.4: Treatments in Study 5[1]



EE = Early escape (patient having < 20% improvement in both tender & swollen joint counts); LE = Long-term extension; R = randomization

1 Patients should have received at least 5 mg oral folic acid weekly during the blinded phase of the study (until the W52 database lock). Stable oral corticosteroids equivalent to $\leq$ 10 mg of prednisone per day and stable marketed NSAID doses were allowed during the blinded phase of the study (until the W52 database lock). However, DMARDs and systemic immunosuppressives were prohibited through W52 of the study and other biologic agents, cytotoxic agents, and investigational agents were prohibited during the entire 5-year study.

Reference: Adapted from amendment 3 of Study 5, Figure 1, Page 20.

DB Period: Patients were randomized 1:1:1:1 to 1 of 4 treatment groups in Study 5 (see Table 9.1.5).

Table 9.1.5: Treatment groups at randomization in the DB, MTX-controlled Period in Study 5

Group #	Therapies	Dosing
Group 1	MTX monotherapy	Oral MTX once weekly[1, 2]
Group 2	golimumab monotherapy	golimumab 100 mg SC once every 4 weeks[1, 2]
Group 3	combination therapy	golimumab 50 mg SC once every 4 weeks & oral MTX once weekly[1,2]
Group 4	combination therapy	golimumab 100 mg SC once every 4 weeks & oral MTX once weekly[1,2]

1 Golimumab was started on Week 0 and then given once every 4 weeks to Week 48. MTX was started at Week 0 at 10 mg once weekly followed by an escalation to MTX 20 mg once weekly by Week 8 and continued 20 mg once weekly to Week 51.
2 Patients may have taken stable doses of concomitant NSAIDs and/or corticosteroids equivalent to ≤ 10 mg prednisone/day during the study.

At Week 28 during the DB Period, any patient who had less than 20% improvement from baseline in both swollen and tender joint counts entered early escape in a double-blinded fashion (see the treatments for the patients who entered escape in Table 9.1.6). Patients who did not enter early escape continued the treatment assigned at randomization.

Table 9.1.6: Treatments for patients who entered escape at Week 28[1] in Study 5

Group #	Treatment prior to escape	Treatment during escape
Group 1	MTX	MTX continued & **golimumab 50 mg SC added** at Week 28 and then every 4 weeks until Week 48[2]
Group 2	golimumab 100 mg SC every 4 weeks	Golimumab 100 mg every 4 weeks continued & **MTX added** at 10 mg once weekly until Week 51[2]
Group 3	golimumab 50 mg SC every 4 weeks & MTX	MTX continued & **golimumab increased to 100 mg SC** at Week 28 and then every 4 weeks until Week 48[2]
Group 4	golimumab 100 mg SC every 4 weeks & MTX	golimumab 100 mg SC continued every 4 weeks & MTX continued **(no change in treatment)**[2]

1 For patients who entered escape at Week 28, they were treated in a double-blind fashion from Week 28 to Week 52.
2 Patients may have taken stable doses of concomitant NSAIDs and/or corticosteroids equivalent to ≤ 10 mg prednisone/day during the study.

LE Period: Treatment during the LE Period started at Week 52 and continued through Week 252 (see Table 9.1.7).

Table 9.1.7: Treatments for patients in the Long-term Extension Period in Study 5[1]

Group #	Treatment prior to LE	Treatment during LE[1]
Group 1	For patients who did not escape and with no swollen or tender joints	MTX continued (**no change**). However, after the 52-week database lock these patients had the **option to add golimumab 50 mg** SC mg every 4 weeks until Week 252 and continue their MTX.
	For patients who did not escape and with ≥ 1 swollen or tender joint	MTX continued & **golimumab 50 mg SC added** starting at Week 52 and then every 4 weeks until Week 252. However, after the 52-week database lock these patients had the **option to increase golimumab to 100 mg SC** once every 4 weeks until Week 252.
	For patients who entered escape	Golimumab 50 mg SC continued every 4 weeks (Weeks 52 to 252) & MTX continued (**no change**). However, after the 52-week database lock these patients had the **option to increase golimumab to 100 mg SC** once every 4 weeks until Week 252.
Group 2	For patients who did not escape	Golimumab 100 mg SC continued every 4 weeks (Weeks 52 to 252). **May have added MTX** after the 52-week database lock[1]
	For patients who entered escape	Golimumab 100 mg SC continued every 4 weeks (Weeks 52 to 252) and MTX continued (**no change**)
Group 3	For patients who did not escape	Golimumab 50 mg SC continued every 4 weeks (Weeks 52 to 252) and MTX continued (**no change**). However, after the 52-week database lock these patients had the **option to increase golimumab to 100 mg SC** once every 4 weeks until Week 252.
	For patients who entered escape	Golimumab 50 mg SC continued every 4 weeks (Weeks 52 to 252) and MTX continued (**no change**)
Group 4	For all patients	Golimumab 100 mg SC continued every 4 weeks (Weeks 52 to 252) and MTX continued (**no change**)

1 The blind was maintained in LE Period until after the last patient finished the 52-week evaluations and the 52-week database was locked. Therefore, during the initial part of LE, the treatments were double-blinded and patients in Group 1 may have received placebo SC injections or sham MTX oral pills.
After the 52-database was locked, the dose of MTX could have been adjusted. After the Week 52 evaluations have been completed, the dosing regimens of concomitant therapy with NSAIDs, corticosteroids, and/or other analgesics may have been adjusted.

Concomitant Medication in Study 5:

MTX: MTX was one of the study agents until the 52-week database was locked. After the 52-week database lock, MTX was not considered as one of the study agents, and the MTX dose could have been adjusted at the investigator's discretion.

Folic Acid/Oral Folinic Acid: All patients should have received at least 5 mg oral folic acid or oral folinic acid weekly at least during the blinded phase of the study (i.e., until the 52-week database lock).

Corticosteroids: Patients treated with oral corticosteroids should have received a stable dose equivalent to
≤ 10 mg prednisone per day for at least 2 weeks prior to their first administration of the study agent and should have continued to receive this dose through Week 52. The dose may have been reduced and the type of oral corticosteroid may have been changed only if the patient developed unacceptable AEs. IM or IV administration of corticosteroids for the treatment of RA was not allowed within 4 weeks prior to and during the study. For patients requiring short courses (2 weeks or less) of oral or IV corticosteroids for reasons such as prophylactic therapy prior to surgery (stress dose

corticosteroids) or therapy for limited infections, exacerbation of asthma, chronic obstructive pulmonary disease, or for any condition other than RA, corticosteroid therapy should have been limited to situations in which, there were no adequate alternatives. Patients may have received an intra-articular injection of a corticosteroid if clinically required at any time during the study. However, the number of intra-articular injections should have been limited to 2 over a 24-week period or 4 during the 52-week period. Corticosteroids administered by bronchial or nasal inhalation for treatment of conditions other than RA may have been given as needed throughout the course of the study.

NSAIDs and other Analgesics: Patients treated with NSAIDs (e.g., nonselective NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors, and aspirin), or other analgesics, should have received the usual marketed doses approved in the country in which the study was conducted, and should have been on a stable dose at least 2 weeks prior to the first administration of the study agent and during the first 52 weeks of the trial. The dose may have been reduced and the type of NSAID or analgesic may have been changed if the patient developed unacceptable AEs. Whenever possible, short-acting NSAIDs and analgesics should not have been administered within 6 hours before study evaluations. Long-acting NSAIDs could have been maintained at their usual dosing intervals before study evaluations. In this trial, aspirin was considered an NSAID, except for low-dose aspirin prescribed for vascular disease.

Disease-modifying Anti-rheumatic Drugs (DMARDs) and Systemic Immunosuppressive Products: DMARDs (other than MTX) and systemic immunosuppressive products were prohibited within the 4 weeks prior to the first administration of the study agent through Week 52 of the study. If any of these prohibited medications were used through Week 52, the patient should have been discontinued from further study agent administration.

Biologic Agents, Cytotoxic Agents, and Investigational Drugs: The use of biologic agents (e.g., anakinra, etanercept, adalimumab, infliximab, alefacept, efalizumab, rituximab, natalizumab), cytotoxic agents (e.g., chlorambucil, cyclophosphamide, nitrogen mustard, other alkylating agents), or investigational drugs was
not allowed during the entire 5-year study including the LE Period. If any of these prohibited medications were used, the patient should have been discontinued from further study agent administration.

Stopping Rules in Study 5: Study agent injections (i.e., golimumab or placebo) were to be permanently discontinued if any of the following occurred:

1. Opportunistic infection.
2. Malignancy, excluding non-melanoma skin cancer.
3. A diagnosis of active TB was made; a patient had symptoms or a chest radiograph suggestive of active TB; or a patient had recent close contact with a person with active TB and could not continue to undergo additional evaluation.
4. A patient who was receiving treatment for latent TB discontinued this treatment prematurely or was noncompliant with the therapy.
5. Bronchospasm with wheezing and/or dyspnea requiring ventilatory support

6. Symptomatic hypotension with a greater than 40 mmHg decrease in systolic blood pressure that occurred following a study agent injection.
7. Symptoms suggestive of serum sickness (e.g., myalgia; arthralgia; fever; rash; pruritus; facial, hand, or lip edema; dysphagia; urticaria; sore throat; and/or headache) occurring 1 to 14 days after an injection of study agent.
8. CHF.
9. Demyelinating disease.
10. Pregnancy or pregnancy planned within the study period or within 6 months after the last study agent injection.
11. The initiation of protocol-prohibited medications (see concomitant medications).
12. Investigator or Centocor's medical monitor deemed it was in the patient's best interest.

Study Monitoring and Evaluation in Study 5: Table 9.1.8 displays the schedule of procedures and evaluations through Week 52 in Study 5. All post-baseline visits through Week 52 must have occurred within ± 7 days.

Table 9.1.8: Schedule of procedures and evaluations through Week 52 in Study 5

Assessments[a]	Screen	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24[b]	Wk 28	Wks 32-48[c]	Wk 52[b]
Consent	X										
Demography/medical history	X										
Physical examination	X							X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	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
Review of entry criteria	X	X									
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Randomization		X									
IVRS notification of tender & swollen joint counts		X							X		X
Study agent injection		X	X	X	X	X	X	X	X	X	X[d]
Study agent injection-site evaluation[g]		X	X	X	X	X	X	X	X	X	X
RA evaluations[h]	X[i]	X	X	X	X	X	X	X	X	X	X
SF-36		X						X			X
HEcon		X		X		X		X		X[j]	X
Radiographs of hands and feet[k]	X								X		X
MRI[k,l]	X				X			X			X[c]
Carotid ultrasound[k,l]	X							X			X[c]
AE review[m]	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[n]	X										
Routine laboratory analyses	X	X	X	X	X	X		X	X	X[o]	X
CRP	X	X	X	X	X	X	X	X	X	X	X
ESR	X[p]	X[p]						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[q]→			
Serum-based PD biomarkers[3]		X	X					X			X
Protein profiling[3]		X	X					X			
Antibodies to golimumab		X						X			X
Cardiovascular biomarkers		X						X			X
Anemia markers		X						X			

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

e Also performed at any time during the study if TB was suspected.
f Long-term extension started 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 was also evaluated at Week 0.
i Only the duration of morning stiffness and joint assessment were performed at screening.
j Performed at Weeks 32, 40, and 48 during this period.
k The initial assessments may have been performed after the screening visit but must have been completed within 4 weeks before first study agent administration.
l Performed at selected sites.
m Also performed for 30 minutes after study agent administration.
n May have been repeated at any time at the discretion of investigator or patient.
o Performed at Weeks 32, 36, 40, and 48 during this period.
p Performed at screening or Week 0.
q One additional sample for serum golimumab concentration was collected from all patients at any time between Weeks 24 and 28 other than at the time of the Week 24 and Week 28 visit; this sample must have been collected at least 24 hours prior to or after a study agent injection.
r Week 52 MRI should have been performed within 7 days before the injection of study agent.
s Week 52 carotid ultrasound should have been performed within 7 days before the injection of study agent.

Efficacy Endpoints in Study 5:

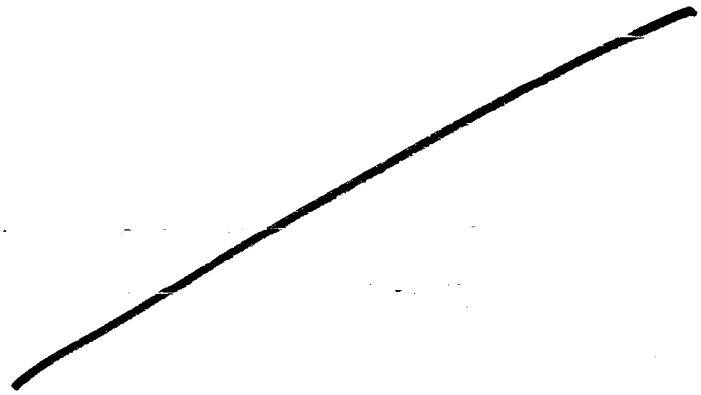
Co-Primary Efficacy Endpoints in Study 5: The co-primary efficacy endpoints were the proportion of patients with an ACR 50 response at Week 24 and the change in baseline in van der Heijde Modified Sharp (vdH-S) score at Week 52.

ACR 50 Response at Week 24: Patients were classified as having achieved an ACR 50 response at Week 24 if both of the following was achieved at Week 24:

1. An improvement of ≥ 50% 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 ≥ 50% from baseline in ≥ 3 of the following 5 assessments:

2.1. Patient's assessment of pain using a Visual Analog Scale (VAS)
2.2. Patient's global assessment of disease activity, using a VAS
2.3. Physician's global assessment of disease activity, using a VAS
2.4. Patient's assessment of physical function as measured by the HAQ disability index
2.5. CRP

Inhibition of Progression of Structural Damage at Week 52: No radiographic data including results of this radiographic endpoint were submitted in the original golimumab BLA. b(4)



b(4)

Secondary Efficacy Endpoints in Study 5: The 4 secondary efficacy endpoints were the following (without a pre-specified order):

1. The proportion of patients who achieved an ACR 20 response at Week 24.
2. Change in HAQ at Week 52: The baseline HAQ disability index score minus the Week 52 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 ≥ 2 component questions and for each of the components, patients were 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 have been adjusted if the patient used an aid, device, or assistance. The highest score recorded by the patient for any component question determined the score for that category. The HAQ was 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.
3. For patients with CRP > 1.0 mg/dL at baseline, the proportion of patients who achieved an ACR 50 response at Week 24.
4. For patients with CRP > 1.0 mg/dL at baseline, the change from baseline in vdH-S score at Week 52.

155 Pre-Specified Endpoints Related to Signs and Symptoms in Study 5: The following were the 155 pre-specified endpoints relating to signs and symptoms:

ACR Response Endpoints

1. 2 endpoints: proportion of patients who achieved an ACR70 and ACR90 response at Week 24.
2. 4 endpoints: proportion of patients who achieved an ACR20, ACR50, ACR70, and ACR90 response at Week 52.

3. 52 endpoints: proportion of patients who achieved an ACR 20, ACR50, ACR70, and ACR90 response over time through Week 52 (i.e., Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52).
4. 1 endpoint: ACR-N index of improvement at Week 24 (see Table 9.1.9).
5. 1 endpoint: proportion of patients who achieved a major clinical response at Week 52 (i.e., met ACR70 response criteria continuously for 6 months)

ACR Component Endpoints

6. 14 endpoints: percent improvement from baseline in each of the 7 ACR components at Week 24 and Week 52
7. 39 endpoints: percent improvement from baseline in swollen joint counts, tender joint counts, and CRP at each visit through Week 52 (13 visits)

Change in DAS

8. 26 endpoints: the change from baseline in DAS 28 (CRP) at each visit through Week 52 (13 visits) and the change in baseline in DAS 28 (ESR) at each visit through Week 52 (13 visits)

DAS Response and Remission Endpoints

9. 2 endpoints: proportion of patients with Disease Activity Index 28 (DAS 28) response using CRP at Week 24 and Week 52. A DAS 28 response at Week 24 was defined as an improvement from baseline at Week 24 > 1.2 or for patients who have ≤ 5.1 at Week 24, an improvement from baseline of > 0.6. A DAS 28 response at Week 52 was defined similarly. The DAS 28 (CRP) instrument includes tender joints (maximum is 28), swollen joints (maximum is 28), CRP, and global health (see Table 9.1.10).
10. 2 endpoints: proportion of patients with DAS 28 response using ESR at Week 24 and Week 52. A DAS 28 response at Week 24 was defined as an improvement from baseline at Week 24 > 1.2 or for patients who have ≤ 5.1 at Week 24, an improvement from baseline of > 0.6. A DAS 28 response at Week 52 was defined similarly. The DAS 28 (ESR) combined tender joints (maximum is 28), swollen joints (maximum is 28), ESR, and global health (see Table 9.1.10).
11. 4 endpoints: proportion of patients with DAS 28 (CRP) remission at Week 24 and Week 52 and the proportion of patients with DAS 28 (ESR) remission at Week 24 and Week 52. A DAS 28 remission at Week 24 was defined as DAS 28 value of < 2.6 at Week 24 (a DAS 28 remission at Week 52 is defined similarly).

ACR Response by PK Endpoints

12. 8 endpoints: Efficacy by PK analysis of the golimumab monotherapy group compared to the combined combination groups. The proportion of patients who achieved an ACR 20 response at Week 24 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 achieved 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 could have been changed based on observed PK data.

Table 9.1.9: ACR-N index

The ACR-N index is defined as the minimum of the following 3 criterion:
1. Percent improvement from baseline in tender joint counts. **2. Percent improvement from baseline in swollen joint counts.** **3. Median percent improvement from baseline for the following 5 assessments: patient's assessment of pain (using VAS), patient's global assessment of disease activity (using VAS), physician's global assessment of disease activity (using VAS), patient's assessment of physical function as measured by the HAQ, and CRP.**

Table 9.1.10: DAS 28 (CRP) and DAS 28 (ESR) formulas

DAS 28 (CRP) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.36 × ln (CRP+1) + 0.014 × GH + 0.96 **DAS 28 (ESR) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.70 × ln (ESR) + 0.014 × GH**
• TEN28 and SW28 are 28 joint counts for tenderness and swelling, respectively. The 28 joint count is based on evaluation of the shoulder, elbow, wrist, metacarpophalangeal (MCP) 1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP) 1, PIP2, PIP3, PIP4, PIP5 joints of both the upper right and left extremities and the knee joints). **• Ln (CRP+1) is natural logarithm of (CRP + 1) and ln (ESR) is the natural logarithm of ESR** **• SQRT is the square root** **• GH is Patient's Global Assessment of Disease Activity on a VAS of 0 (very well) to 100 (very poor) mm.**

Other Pre-Specified Endpoints in Study 5: There were numerous other pre-specified endpoints relating to physical function, joint structural damage, cardiovascular safety (e.g., cardiovascular adverse reactions, cardiovascular markers, carotid ultrasound results), MRI of the wrists and MCPs, and SF-36.

Statistics in Study 5:

Populations: The pre-specified populations were:

1. **Intent-to-Treat (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.

Database Locks: The 4 database locks in Study 5 occurred or will occur at Weeks 24, 52, 104, and 268 after all patient evaluations through Weeks 24, 52, 104, and 268, respectively.

Methods for the ACR50 and Radiographic 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 (the analysis of structural damage endpoint will be performed contingent upon the positive test result in reduction of signs and symptoms endpoint):

1. Proportion of patients who achieve an ACR50 response at Week 24
2. Change from baseline in vdH-S score at Week 52

There was four-tiered testing for the first co-primary efficacy endpoint (i.e., ACR 50 response at Week 24):

1. The primary statistical comparison (for superiority), using a 2-sided ($\alpha = 0.05$) Cochran-Mantel-Haenszel (CMH) test stratified by screening CRP (< 1.5 mg/dL; ≥ 1.5 mg/dL), was 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 was 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 was be performed.
3. If "positive tests results for the analysis" presented above were achieved then a non-inferiority analysis between the golimumab and MTX monotherapy groups was performed. Non-inferiority of golimumab and MTX was demonstrated if the lower bound of the 95% confidence interval (CI) was above -0.1.
4. If non-inferiority was declared, then a superiority analysis, using a 1-sided ($\alpha = 0.025$) CMH test stratified by screening CRP (< 1.5 mg/dL; ≥ 1.5 mg/dL), between the golimumab and MTX groups was performed.

According to the SAP, a positive trial constituted a positive test result for the first co-primary efficacy endpoint (i.e., ACR 50 response at Week 24). A positive test result for this endpoint was defined as a statistically significant global test (i.e., combined low and high dose combination groups versus the MTX monotherapy group) **and** at least one statistically significant pair-wise test (low-dose combination group with MTX **or** the high-dose combination group with MTX).

Handling of Treatment Failure, Dropouts, and Missing Data for the ACR 50 Primary Efficacy Endpoint: Patients who met either of the following treatment failure criteria prior to Week 24 were considered to not have achieved an ACR 50 response:

1. Initiation of DMARDs; systemic immunosuppressive products; biologics; or oral, IV, or IM steroids for RA or an increase the dose of oral corticosteroids for RA above the baseline dose;
2. Discontinuation of study agent injections due to an unsatisfactory therapeutic effect.

Patients with missing data for all of the ACR components at Week 24 will be considered as ACR50 non-responders at Week 24. If patients have missing data but have data for ≥ 1 ACR component at Week 24, the following rules were applied in the specified order:

1. For any ACR component, if **all the component values** were missing from baseline through Week 24, the percent improvement from baseline at Week 24 will be imputed with 0%.
2. For any ACR component, if the **component value at Week 24** is missing, the missing component was replaced by the last non-missing observation (LOCF).
3. For any ACR component, if the **component value at baseline was missing**, the median component value of all patients in the same stratum (screening CRP < 1.5 mg/dL; ≥ 1.5 mg/dL) at baseline was assigned.

If patients had a joint injection and/or surgical joint procedure (e.g., prior to the date of randomization or during the study), the following rules were applied for **joint evaluations**:

1. For patients with a joint injection or surgical joint procedure prior to the date of randomization, the affected joints were analyzed according to the impact of the joint injection and/or surgical joint procedure on the evaluability of the involved joints (see Table 9.1.11). If a joint was considered unevaluable at baseline due to certain procedure/injection performed prior to the date of randomization, the joint was considered unevaluable throughout the study. For patients who had an incomplete set of evaluable tender or swollen joints, the joint count was adjusted (i.e., dividing the number of affected joints by the number of evaluable joints and multiplying by 68 for tender joints or 66 for swollen joints).
2. For patients undergoing surgical joint procedures during the study for RA, the affected joints were to be considered as swollen and tender from the date of procedure onwards.
3. For patients undergoing joint injections during the study, the affected joints were to be considered as swollen and tender from the date of injection for the next 90 days.

Table 9.1.11: Evaluability of joints following a joint procedure or injection prior to randomization in Study 5

Procedure/injection	Impact on joint count outcome
Synovectomy	Not evaluable
Arthrodesis	Not evaluable
Joint replacement	Not evaluable
Amputation	Not evaluable
Arthrocentesis	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Steroid injection	Evaluable if happened > 3 months prior to randomization, otherwise not evaluable
Excision	Not evaluable
Arthroscopy-surgery	Evaluable if happened > 3 months prior to randomization, otherwise not evaluable
Arthroscopy-diagnose	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Bunionectomy	Not evaluable
Chondroplasty	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Synovial cyst	Evaluable if happened > 4 weeks prior to randomization, otherwise not evaluable
Needle biopsy	Evaluable if happened > 3 months prior to randomization, otherwise not evaluable
Osteotomy	Not evaluable
Radiosynovectomy	Not evaluable
Arthrotomy	Not evaluable
Fracture reduction	Not evaluable
Tendon surgery	Not evaluable
Bursal surgery	Not evaluable

Reference: Adapted from the SAP of Study 5, amendment 1, Appendix 1.1, Page 92

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

Methods for the Secondary Efficacy Endpoints: Analyses of the 4 secondary efficacy endpoints were only be considered if positive test results were achieved for the first primary efficacy endpoint (i.e., ACR50 response at Week 14). There were 4 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 155 pre-specified signs and symptoms endpoints or the numerous other endpoints relating to physical function, joint structural damage, cardiovascular (e.g., cardiovascular adverse reactions, cardiovascular markers, carotid ultrasound results), MRI of the wrists and MCPs, and the SF-36.

Results of the 24-Week Efficacy Data and 52-Week Safety Data for Study 5:

Study 5 Dates Conducted: December 12, 2005 was the study start date (i.e., the date of first patient enrollment) and October 1, 2007 was the date that the last patient completed Week 24. The long-term extension of Study 5 is ongoing.

Disposition: Table 9.1.12 displays the patient disposition through Week 24 in Study 5. Since the evaluation for early escape occurred at Week 28 in the one-year controlled treatment period in Study 5, none of the patients entered early escape through Week 24.

The proportion of patients who discontinued the SC study agent (i.e., placebo, golimumab50, or golimumab100) was similar in the four treatment groups. A greater proportion of patients in the golimumab combination groups, compared to patients in the MTX and golimumab monotherapy groups, discontinued the SC study agent due to an adverse event (DAE) — see Table 9.1.23.

A greater proportion of patients who received MTX (i.e., the MTX monotherapy group and the golimumab combination groups) had a DAE compared to patients who received oral placebo tablets (i.e., golimumab monotherapy group).

Table 9.1.12: Patient disposition through Week 24 in Study 5

	Monotherapy Groups		Combination Groups	
	MTX n (%)	Golimumab100 n (%)	Golimumab50 & MTX n (%)	Golimumab100 & MTX n (%)
Randomized[1]	160 (100%)	159 (100%)	159 (100%)	159 (100%)
Received ≥ 1 dose of SC agent[2]	160 (100%)	157 (99%)	158 (99%)	159 (100%)
Ended study participation	10 (6%)	11 (7%)	9 (6%)	8 (5%)
Discontinued SC study agent	10 (6%)	9 (6%)	8 (5%)	10 (6%)
Adverse event	1 (1%)	1 (1%)	6 (4%)	7 (4%)
Other	5 (3%)	5 (3%)	1 (1%)	2 (1%)
Lost to follow-up	3 (2%)	0 (0%)	1 (1%)	1 (1%)
Unsatisfactory therapeutic effect	1 (1%)	3 (2%)	0 (0%)	0 (0%)
Discontinued PO study agent	12 (8%)	10 (6%)	9 (6%)	10 (6%)
Adverse event	3 (2%)	1 (0.6%)	6 (4%)	8 (5%)
Other	4 (3%)	5 (3%)	1 (1%)	1 (1%)
Lost to follow-up	3 (2%)	0 (0%)	1 (1%)	1 (1%)
Discontinued SC study agent administration	1 (1%)	2 (1%)	1 (1%)	0 (0%)
Unsatisfactory therapeutic effect	1 (1%)	2 (1%)	0 (0%)	0 (0%)

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 to 20 mg by Week 20)

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

2 The treated statistical population was the primary statistical population for all the safety analyses and clinical pharmacology analyses (i.e., patients who received ≥ 1 dose of SC agent). Two patients in the golimumab100 monotherapy group and one patient in the low dose combination group were randomized and never treated because they all withdrew consent.

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

Protocol Deviations: Table 9.1.13 displays the protocol deviations through Week 24 in Study 5. 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 9.1.13: Protocol deviations in Study 5 through Week 24

	Monotherapy Groups		Combination Groups	
	MTX (n=160)	Golimumab100 (n=159)	Golimumab50 & MTX (n=159)	Golimumab100 & MTX (n=159)
Patients who did not meet eligibility criteria	6%	9%	6%	9%
Patients with SC study agent administration deviation	14%	26%	15%	15%
Received administration outside protocol-specified window	11%	20%	11%	10%
Missed an administration	4%	8%	4%	4%
Received an incorrect study agent or incorrect dose	0%	0%	0%	1%
Patients with PO study agent administration deviation	23%	38%	35%	36%
Missed an administration	15%	27%	24%	23%
Received an incorrect study agent or incorrect dose	13%	17%	14%	17%

Reference: Adapted from Final Study Report for Study 5, Table 7, Page 75; Table 8, Page 77; Table 10, Page 80.

Demographics: Table 9.1.14 displays the baseline demographics in Study 5.

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 is probably a reflection of the countries that participated in this study (e.g., about 19% of the patients in the study were Asian and about 19% of the patients were from Asian countries). In Study 5, about 82% and 18% of the patients lived in non-U.S. and U.S. countries, respectively. Since many patients with RA in the United States have received MTX, it may have been difficult to enroll this RA subpopulation in the United States.

Table 9.1.14: Baseline demographics at baseline in Study 5[1]

		Monotherapy Groups		Combination Groups	
		MTX (n=160)	Golimumab100 (n=159)	Golimumab50 & MTX (n=159)	Golimumab100 & MTX (n=159)
Age	Mean (SD)	49 (13) years	48 (13) years	51 (11) years	50 (12) years
Sex	Male	16%	16%	15%	21%
	Female	84%	84%	85%	79%
Race	Caucasian	71%	70%	75%	74%
	Asian	16%	20%	19%	20%
	Other	9%	8%	6%	6%
	Black	4%	3%	1%	1%
Weight	Mean (SD)	72 (18) kg	72 (21) kg	73 (18) kg	71 (17) kg
Height	Mean (SD)	163 (9) cm	162 (9) cm	162 (9) cm	163 (9) cm
Country[2]	Europe, Australia, New Zealand, & Canada	46%	43%	45%	43%
	Latin America	21%	18%	19%	20%
	United States	17%	18%	18%	18%
	Asia	16%	19%	18%	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 20 mg of oral MTX given once weekly (starting dose of MTX 10 mg and then escalation to 20 mg by Week 20)

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

2 The European subgroup includes European countries (i.e., Austria, Belgium, Hungary, Italy, Poland, Russia, Spain, Ukraine, and the UK), New Zealand, Australia, and Canada. Asian countries included India, Malaysia, the Philippines, Singapore, Korea, Taiwan, and Thailand. Latin American countries included Argentina and Chile.

Reference: Adapted from Final Study Report for Study 5, Table 12, Pages 84-85. Also adapted from the demographic JMP dataset from Study 5.

Baseline Disease Characteristics: Table 9.1.15 displays the baseline disease characteristics in Study 5.

The baseline disease characteristics in Study 5 were similar in the four treatment groups. The four treatment groups had similar disease activity as measured by the DAS28 (CRP) and the ACR core components. In Study 5, 19% of patients had a prior joint injection or procedure, the mean duration of RA disease was 3.5 years, the mean duration of morning stiffness was 2.9 hours, the mean number of swollen joints was 16, and the mean number of tender joints was 28. 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 9.1.15: Baseline disease characteristics of RA in Study 5[1]

		Monotherapy Groups		Combination Groups	
		MTX (n=160)	Golimumab100 (n=159)	Golimumab50 & MTX (n=159)	Golimumab100 & MTX (n=159)
Disease duration, mean (SD)		2.9 (4.8) years	4.1 (5.6) years	3.5 (5.6) years	3.6 (6.1) years
Received MTX in past		0%	0%	0%	0%
Prior joint procedure or injections		21%	18%	14%	21%
Duration of morning stiffness, mean (SD)		3.8 (5.6) hours	2.7 (4.3) hours	2.5 (3.5) hours	2.5 (3.8) hours
Extra-articular manifestations[2]	Rheumatoid nodules	12%	7%	9%	7%
	Sicca syndrome	8%	7%	4%	4%
	Other	4%	6%	5%	3%
	Peripheral neuropathy	1%	3%	1%	2%
	Interstitial lung fibrosis	1%	1%	2%	1%
	Vasculitis	1%	0%	1%	1%
	Lymphadenopathy	1%	1%	0%	0%
Anatomical stage	Stage I	26%	30%	29%	26%
	Stage II	52%	46%	51%	54%
	Stage III	18%	22%	17%	16%
	Stage IV	3%	3%	3%	4%
Functional class	Class I	17%	15%	17%	17%
	Class II	56%	57%	56%	57%
	Class III	23%	26%	25%	23%
	Class IV	4%	3%	3%	3%
ACR Core Set (median)	# of swollen joints (0-66)	11	12	13	14
	# of tender joints (0-68)	26	25	26	26
	Pain assessment (patient)[3]	7	7	7	7
	Disease activity (patient)[3]	6	7	6	6
	Disease activity (physician)[3]	6	6	6	6
	HAQ disability index (0-3)	1.5	1.8	1.5	1.6
	CRP mg/dL	1.4	1.3	1.3	1.3
# of swollen joints (0-66), mean (SD)		15 (10)	15 (10)	16 (10)	16 (10)
# of tender joints (0-68), mean (SD)		27 (16)	27 (15)	29 (17)	27 (15)
Other Characteristics	DAS28 (CRP), median	5.0	5.1	5.1	5.1
	Positive anti-CCP antibodies	76%	79%	67%	73%
	Positive rheumatoid factor	82%	81%	76%	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 20 mg of oral MTX given once weekly (starting dose of MTX 10 mg and then escalation to 20 mg by Week 20)

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

2 Baseline extra-articular manifestations at were included if ≥ 2 patients in any one group that had that manifestation. No patient in any group had pericarditis, amyloidosis, splenomegaly, or Felty's syndrome at baseline.

3 Measured on a 0-10 cm VAS scale

Reference: Adapted from Final Study Report for Study 5, Table 13, Pages 87-88, Table 14, Pages 89-90; Table 1.13, Pages 235-236

Prior Medications: Table 9.1.16 presents the proportion of patients who received DMARDs, immunosuppressive products, corticosteroids, and/or NSAIDs prior to enrollment in Study 5.

There were no significant differences in the proportions of patients who received DMARDs, immunosuppressive products, anakinra, steroids, or NSAIDs in the four treatment groups. Even

though only 2 (0%) patients received MTX in the past, 55% of patients received at least one non-MTX DMARD in the past (e.g., sulfasalazine, hydroxychloroquine, chloroquine, leflunomide) and 67% of patients received systemic corticosteroids in the past. The patients in Study 5 were MTX-naive but they were not DMARD-naive.

Table 9.1.16: Percent of patients who received DMARDs, immunosuppressive products, corticosteroids, and/or NSAIDs prior to enrollment in Study 5[1]

	Monotherapy Groups		Combination Groups	
	MTX (n=160)	Golimumab100 (n=159)	Golimumab50 & MTX (n=159)	Golimumab100 & MTX (n=159)
Received ≥ 1 MTX[2]	0%	0%	0%	0%
Received ≥ 1 non-MTX DMARD	52%	59%	50%	57%
Sulfasalazine	32%	34%	23%	31%
Hydroxychloroquine	16%	27%	21%	25%
Chloroquine	11%	6%	9%	7%
Leflunomide	8%	9%	8%	7%
Other DMARDs	3%	9%	5%	4%
Gold preparations	3%	5%	4%	6%
Penicillamine	0%	0%	2%	2%
Received ≥ 1 immunosuppressive	2%	4%	1%	6%
Cyclosporine	1%	2%	1%	2%
Azathioprine	1%	1%	0%	3%
Other immunosuppressives	0%	1%	1%	1%
Tacrolimus	0%	0%	0%	1%
Mycophenolate mofetil	0%	0%	0%	0%
Received anakinra	0%	0%	0%	1%
Received systemic corticosteroids	68%	64%	70%	65%
Received NSAIDs	96%	98%	98%	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 20 mg of oral MTX given once weekly (starting dose of MTX 10 mg and then escalation to 20 mg by Week 20).

1 The ITT statistical population was the primary statistical population for the efficacy analyses (i.e., patients randomized regardless of whether or not they receive the assigned treatment). In Study 5, 45% of patients never received a DMARD in the past and 4% of patients in Study 5 received ≥ 3 DMARDS in the past.

2 Only 1 patient in the golimumab50 & MTX group and 1 patient in the golimumab100 & MTX group received MTX in the past.

Reference: Adapted from Final Study Report for Study 5, Table 1.19, Page 249-250; Table 1.20, Pages 251-255; also adapted from concomitant medication JMP dataset from Study 5.

Steroid and/or NSAID Use at Baseline: Table 9.1.17 displays the percent of patients who received corticosteroids and/or NSAIDs at baseline in Study 5. Patients were considered to be taking corticosteroids or NSAIDs at baseline in Study 5 if they had been used prior to **and** after the first study agent administration. The data in Table 9.1.16 differs from the data in Table 9.1.15 which displays the proportion of patients who received treatments for RA prior to enrollment. Also Table 9.1.15 displays the percent of patients who received systemic steroids; whereas, Table 9.1.16 displays the percent of patients who received oral steroids.

A similar proportion of patients in the four treatment groups received corticosteroids and/or NSAIDs at baseline and at Week 24 in Study 5. For the patients who received steroids at baseline and at Week 24, the mean dose of prednisone was similar in the four treatment groups.

Table 9.1.17: Percent of patients who received corticosteroids and/or NSAIDs at baseline and at Week 24 in Study 5[1]

	MTX (n=160)	Golimumab100 (n=159)	Golimumab50 & MTX (n=159)	Golimumab100 & MTX (n=159)
Received oral corticosteroids at baseline	**52%**	**54%**	**52%**	**50%**
For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	**6 (2) mg**	**7 (2) mg**	**7 (3) mg**	**7 (3) mg**
Received NSAIDs at baseline	**84%**	**84%**	**84%**	**87%**
Received oral corticosteroids at baseline	**53%**	**54%**	**50%**	**49%**
For patients who received steroids, mean (SD) daily dose of prednisone or equivalent	**7 (4) mg**	**7 (6) mg**	**7 (3) mg**	**8 (6) mg**
Received NSAIDs at baseline	**82%**	**79%**	**77%**	**86%**

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 to 20 mg by Week 20).

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

Reference: Adapted from Final Study Report for Study 5, Table 1.21, Page 256 and also adapted from Response to Information Request (Submission #2), Table 1, Page 6.

Sign and Symptom Efficacy Results: Table 9.1.18 displays the major sign and symptom efficacy results in Study 5. The pre-specified primary efficacy endpoint (highlighted in yellow in the table below) was the proportion of patients who had an ACR 50 response at Week 24, using the randomized patient population.

Although the combined low and high dose combination groups (i.e., golimumab50 & MTX and golimumab100 & MTX) had a greater proportion of ACR 50 responders (the primary efficacy endpoint), compared to the MTX group (using the pre-specified randomized patient population), this was not statistically significant. Using a post-hoc statistical population (i.e., all treated patients), the low dose combination group (i.e., golimumab50 & MTX) is superior to the MTX group in the proportion of ACR 50 responders. The difference between the randomized and treated populations for this analysis was one randomized patient in the low dose combination group that was not treated.

Both the low and high combination groups, compared to the MTX group, had greater proportions of ACR 20 responders, ACR 70 responders, and ACR-N responders at Week 24. In addition, the change from baseline in the DAS28 (CRP) at Week 24 was greater in the both the low and high combination groups, compared to the MTX group.

The high dose combination group did not have improved responses compared to the low dose combination groups (i.e., there was no evidence of dose response). The golimumab monotherapy group appeared to have similar responses as the MTX control group.

The four treatment groups had similar baseline disease activity as measured by DAS28 (CRP). The golimumab combination groups compared to the golimumab and MTX monotherapy groups had lower disease activity at Week 24. There was no evidence of a dose response between the low and high dose golimumab combination groups.

Table 9.1.18: Major sign and symptom efficacy results at Week 24 in Study 5

		Monotherapy Groups		Combination Groups		
		MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX	Combined
Randomized patients[1]		160	159	159	159	318
ACR 20 responders[2]		49%	52%	62%	62%	62%
p-value (versus MTX)		—	0.677	0.028	0.028	0.011
ACR 50 responders[3]		29%	33%	40%	37%	38%
p-value (versus MTX)		—	0.521	0.042	0.177	0.053
ACR 70 responders		16%	14%	24%	18%	21%
ACR-N Index, mean (SD)		20 (48)	21 (47)	28 (70)	27 (51)	28 (61)
Treated patients[4]		160	157	158	159	317
ACR 50 responders		29%	33%	41%	37%	39%
p-value (versus MTX)		—	0.473	0.038	0.177	0.049
Patients with W24 DAS (CRP)		150	144	152	148	300
DAS28 (CRP)[5], mean	Baseline	5.0	5.1	5.1	5.1	5.1
	Week 24	3.5	3.5	3.2	3.1	3.2
	Change	1.5	1.6	1.9	2.0	1.9

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 to 20 mg by Week 20). The combined group includes both combination groups (golimumab100 & MTX and golimumab50 & MTX)

1 All randomized patients were the primary statistical population for the efficacy analyses.

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

3 The primary efficacy endpoint in Study 5 was the proportion of patients who had an ACR 50 response at Week 24, using the randomized patient population.

4 All treated patients were a post-hoc statistical population for the efficacy analyses (all treated patients was the primary statistical population for the safety population). There were 3 patients in Study 5 who were randomized but not treated (i.e., 2 patients in the golimumab100 monotherapy group and 1 patient in the low dose combination group).

5 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. The change from baseline in the DAS 28 (CRP) at Week 24 was performed with only observed data at Week 24, without imputation. This endpoint was 1 of 155 other sign and symptoms endpoints in Study 5.

Reference: Adapted from Final Study Report for Study 5, Table 17, Page 107, Table 18, Page 110, Table 3.5, Page 421; Table 18, Page 110; Table 3.16 Page 432; Table 3.21, Pages 442; Table 3.26, Pages 447-448; and from Study 5 VISRA datasets.

Table 9.1.19 displays the change from baseline in each ACR component at Week 24 in Study 5.

Both the low and high dose combination groups had a greater percentage of improvement in the 7 ACR components compared to the MTX and golimumab monotherapy groups. There was no clear dose response. The MTX monotherapy group, compared to the golimumab monotherapy group, had a similar to slightly greater percent change of improvement from baseline in the 7 ACR components.