3/11/09

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125289/000
Drug Name:	Golimumab
Indication:	In combination with methotrexate, [redacted] adult patients with moderate to severely active rheumatoid arthritis. b(4)
Applicant:	Centocor
Date(s):	Stamp Date: 6/24/2008
	PDUFA Date: 4/24/2009
Review Priority:	Standard
Biometrics Division:	DBII
Statistical Reviewer:	Jonathan Norton
Concurring Reviewers:	Dionne Price
	Thomas Permutt
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical Team:	Eric Brodsky
Project Manager:	Sharon Turner-Rinehardt

Keywords: add-on design, blinding, clinical studies, Cochran-Mantel-Haenszel, double-blind, missing data, sensitivity analyses

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Golimumab is a human monoclonal antibody that is purported to reduce the activity of human tumor necrosis factor alpha (TNFα). The Applicant seeks to have golimumab licensed for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. The proposed dosage is 50 mg per month, to be delivered subcutaneously using either an autoinjector or a pre-filled syringe. The scope of this review is the indication "[redacted] adult patients with moderate to severely active rheumatoid arthritis", for which golimumab is to be given in combination with methotrexate (MTX). b(4)

I find that the totality of the evidence indicates that the 50 mg dose of golimumab is effective for the RA indication when used in combination with methotrexate.

1.2 Brief Overview of Clinical Studies

The application is based on three pivotal studies. Study C0524T05, also known as GO-BEFORE, was a double-blind, placebo-controlled study of golimumab in MTX-naïve patients with active rheumatoid arthritis. The study was conducted at 90 sites in multiple regions of the world; 18 sites were domestic. Six hundred thirty-seven subjects were randomized into four groups in roughly equal proportions: injected placebo + MTX, golimumab 100 mg + oral placebo, golimumab 50 mg + MTX, golimumab 100 mg + MTX. Golimumab/placebo injections were given every four weeks, and MTX/placebo pills were given weekly. The MTX dose started at 10 mg and was escalated to 20 mg. The primary efficacy endpoint for the indication currently under review (signs and symptoms) was the American College of Rheumatology (ACR) 50 response at Week 24. Major secondary endpoints (as specified by the Applicant) included the ACR 20 response at week 24 and the primary endpoint restricted to patients with abnormal C-reactive protein (CRP) at baseline.

Study C0524T06, also known as GO-FORWARD, was similar in design to the GO-BEFORE study but targeted patients with active RA despite treatment with MTX. The study was conducted at 65 sites throughout the world. In the study, 444 subjects were randomized to the following four treatment groups in a 3:3:2:2 ratio: placebo + MTX (n =133), golimumab 100 mg + placebo (n =133), golimumab 50 mg + MTX (n = 89), and golimumab 100 mg + MTX (n = 89). As with the GO-BEFORE study, injections were given every four weeks and pills were taken weekly. In contrast to the uniform dosing in the GO-BEFORE study, subjects in this study who received active MTX were given the stable weekly dose that they used at baseline. The primary endpoints in this study were the proportion of subjects who had an ACR 20 response at Week 14 and the improvement from baseline in the health assessment questionnaire (HAQ) score at Week 24. These endpoints are described as "co-primary", but the protocol specified that the HAQ would not be considered a primary endpoint without a positive response on the ACR 20. Major secondary endpoints included the Disease Activity Score (DAS) at Week 14, the ACR 20 response at Week 24, and the improvement from baseline in HAQ at Week 14.

Study C0524T11, also called GO-AFTER, targeted subjects who had previous been treated with biologic anti-TNFα agent(s). The study was conducted at 101 sites in North America, Europe, and Australia/New Zealand. Four hundred sixty-one (461) subjects were randomized to the following treatments: placebo (n=155), golimumab 50 mg (n=152), and golimumab 100 mg (n=152). Golimumab was not given as a monotherapy; subjects were allowed to stay on a variety of background therapies including MTX. Injections were given every four weeks. The primary endpoint was the proportion of patients achieving an ACR 20 response at Week 14. Major secondary endpoints included ACR 50 at Week 14, the DAS28 at Week 14, the ACR 20 at Week 24, and improvement in HAQ score at Week 24.

The GO-FORWARD and the GO-AFTER studies allowed for early escape at Week 16. Subjects qualified if they showed less than 20% improvement in both the swollen and the tender joint counts. These subjects were switched to either a higher dose or an additional active drug, depending on their original treatment.

1.3 Statistical Issues and Findings

The primary efficacy analysis in the GO-BEFORE and GO-AFTER studies was a Cochran-Mantel-Haenszel (CMH) test on the ACR response. In the former study it was stratified by baseline CRP, in the latter by baseline MTX use. The GO-FORWARD study had two primary analyses: a Pearson chi-square test on the ACR 20 and a van der Waerden normal scores test on the HAQ. A gatekeeping strategy was used to control multiplicity across doses and, for the GO-FORWARD study, endpoints. Imputation was primarily last-observation-carried-forward (LOCF) but incorporated some conservative features. Early escape was handled appropriately.

Taken at face value, the results from the GO-FORWARD and GO-AFTER studies demonstrated clear statistical support for the efficacy of golimumab in combination with either MTX or other background therapy. In these studies, the only treatment that was not superior to its control was the golimumab 100 mg-only treatment in the GO-FORWARD study.

The results of the GO-BEFORE study were somewhat more equivocal. The planned gatekeeping sequence was to test whether the combined golimumab + MTX group (both 50 mg and 100 mg doses) was superior to MTX alone at the .05 level, then to test the individual doses at the level only if that test was significant. In the study, the p-value for the combined group was .053. If one continues on to test the individual doses of golimumab + MTX, then the p-values are .042 for the 50 mg dose and .177 for the 100 mg dose. From a strict standard of type I error control, one is not permitted to conclude from this study that golimumab 50 mg + MTX was superior to MTX alone. As a matter of judgment, I do not think it necessary to dismiss the evidence from this study on the basis of an additional 3/1000 risk of committing a type I error. The results are supportive of the other two studies.

Although the accumulated statistical results from these studies were supportive of efficacy on their face, there were potential sources of bias which were considered before a definitive conclusion was reached. First of all, there were irregularities in study drug administration that were caused to an undermined degree by a clinical supply shortage. These irregularities include both missed doses and doses taken out-of-window, and were found for both the injected

treatments (golimumab and placebo) and oral treatments (methotrexate and placebo). Based on *a priori* reasoning, the missed injections should only introduce bias in favor of the null hypothesis of no difference, if they introduce bias at all. A patient in the control group who misses an injection is only losing the placebo effect, while a patient in the golimumab group would lose both the placebo effect and the biological effect of golimumab. The effect of missed oral treatments is less clear, however, as subjects in the control group received active pills. In principle, a substantial excess of missed MTX doses in the control group (i.e., less total exposure) would bias the results against the null hypothesis. For two of the studies, GO-BEFORE and GO-AFTER, the information provided by the Applicant shows that this was not the case. No information on missed oral doses was provided for the third study, but based on randomization one would not expect a substantial difference between treatment groups. Following the reasoning in the foregoing sentences as well as considering the results of a battery of sensitivity analyses, I concluded that the missed doses do not undermine a finding of efficacy.

In addition to the incidents of missed doses, the Applicant also reported that a number of injected doses were given out-of-window. After discussion with Eric Brodsky, M.D., I concluded that since golimumab works over a relatively long time scale it is unlikely that these deviations would have biased the efficacy analysis.

In addition to the effects of missed or out-window doses, there was another potential concern that arose from the supply shortage. As a hypothetical scenario, one might envision an investigator becoming unblinded in regard to a subject's treatment on the basis of the availability of study medication for that subject. In response to an information request, however, the Applicant gave written assurances that this was not possible due to the procedures used to maintain the blind.

A final concern that arose in regard to the clinical studies is that the Applicant used a type of biased coin randomization. This class of methods seeks to minimize the imbalance of treatment assignments across stratification factors by identifying the treatment assignment for a particular subject that would yield the best balance given prior assignments, then giving that treatment the highest probability of selection. While biased coin randomization yields the desirable result of better balance, it can potentially invalidate the results of conventional statistical tests which assume completely random assignment.

The Applicant addressed this concern by conducting ***re-randomization tests***. In a standard re-randomization test, subjects retain their original outcomes but are randomly assigned new treatments using the same algorithm that was used in the original study. In particular, the original order of entry is used when making the new random assignments. The randomization is replicated many times and the null distribution of the test statistic is estimated. Comparing the actual test statistic to the null distribution then yields a valid p-value. The Applicant conducted this type of test for the primary outcome of the GO-AFTER study, and the results were supportive of those from the conventional tests.

The usual re-randomization test, as described in the previous paragraph, could not be used for the GO-BEFORE and GO-FORWARD studies. The reason is that those studies had an extra golimumab-only arm that is not relevant to the comparison of primary interest, that of golimumab in combination with MTX to MTX alone. The presence of this extra arm changes the

interpretation of the usual re-randomization test. To get around this problem, the Applicant used a novel ***weighted re-randomization*** method. Using this method, the randomization was forced so that subjects originally assigned to golimumab monotherapy kept that assignment in each replication. Weights were then used to compute a p-value that is purported to be valid despite the forced randomization. The Applicant's new method appears adequate for the present purpose, and the results of weighted re-randomization tests on the primary ACR outcomes were supportive of the results from the conventional tests.

2. INTRODUCTION

2.1 Overview

Golimumab is a human monoclonal antibody that is purported to reduce the activity of tumor necrosis factor alpha (TNFα). The Applicant seeks to have Golimumab licensed for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. The proposed dosage form is a 50 mg subcutaneous injection, delivered in a single-use autoinjector or a pre-filled syringe. Golimumab has not been previously licensed in the United States for any indication. This scope of this review includes the Phase 3 studies supporting the indication "[redacted] adult patients with moderate to severely active rheumatoid arthritis," as shown in Table 1.The Applicant submitted data through Week 24 of each study.

b(4)

Table 1: Overview of Phase 3 Studies

Study ID	Study Design	Population and Sample Size	Primary Endpoint(s) and Results
C0524T05 GO-BEFORE	Multi-center, placebo-controlled, 4-arm parallel study of golimumab alone or in combination w/ MTX	Subjects with active RA who have ***not*** been previously treated with MTX 637	*ACR 50 at Week 24* In combined 50 mg and 100 mg dose groups, golimumab + MTX marginally better than MTX alone (p = .053) 50 mg dose + MTX found superior to MTX (.042), but 100 mg dose + MTX not superior.
C0524T06 GO-FORWARD	Multi-center, placebo-controlled, 4-arm parallel study of golimumab alone or in combination w/ MTX	Subjects with active RA despite MTX therapy 444	*ACR 20 at Week 14* In both 50 mg and 100 mg dose groups, golimumab + MTX better than MTX alone (p < .001) *Improvement in HAQ at Week 24* In both 50 mg and 100 mg dose groups, golimumab + MTX better than MTX alone (p < .001)
C0524T11 GO-AFTER	Multi-center, placebo-controlled, 3-arm parallel study of golimumab	Subjects with active RA who have been previously treated with biologic anti-TNFα agents 461	*ACR 20 at Week 14* In both 50 mg and 100 mg dose groups, golimumab better than placebo (p < .001)

In an End of Phase 2 teleconference on March 8, 2005, the Division of Therapeutic Biologic Internal Medicine Products (DTBIMP) addressed several questions from the Applicant about the planned RA studies. When asked about the general dosing schedule for the Phase 3 program, DTBIMP requested that in the BLA the Applicant provide "adequate data and analyses" to assess whether fixed-dosing provides similar efficacy and safety for different body weights. The Applicant also asked about a general procedure in three-arm studies of first comparing the combined dose groups to the control group, then comparing each dose to control only if the first comparison was significant. DTBIMP noted that under this procedure, "If the null hypothesis is not rejected in the test for the combined groups, then it is not permissible to continue even if an informal assessment suggests that one of the dose groups v. placebo comparisons is significant."

In regard to the proposed C0524T05 study, at this meeting DTBIMP recommended the addition of a golimumab monotherapy arm so that the contribution of MTX to the therapeutic effect could be assessed. The proposed primary endpoint, ACR 50 at Week 24, was deemed acceptable, and DTBIMP also stated that a significant improvement in the ACR 20 would not be required. DTBIMP also agreed with the Applicant's plan to allow early escape at Week 28.

In regard to protocol C0524T06, DTBIMP agreed "in principle" with the proposed primary endpoint of ACR 20 at Week 14, with ACR 20 at Week 24 a "major secondary endpoint" to show maintenance of effect and with an allowance for early escape at Week 16 (these subjects being considered non-responders at Week 24). There was also extensive discussion of the requirements to make a monotherapy claim for golimumab.

Protocol C0524T11 had not been submitted at the time of the March 2005 meeting. Following a reorganization within FDA, golimumab fell within the purview of the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). In a letter of April 5, 2006, DAARP indicated that the protocol ' b(4)

A pre-BLA meeting was held with DAARP on August 21, 2007. At this meeting there was extensive discussion of a sequential test procedure to establish the efficacy of golimumab monotherapy. Also discussed was the proper way to assess the effect of a study agent supply shortage (affecting both golimumab and MTX) on the studies. DAARP requested a sensitivity analysis based on excluding subjects who missed at least 3 consecutive doses of MTX or at least 1 dose of golimumab due to the supply problem. The Applicant replied that their records do not indicate the reason why a dose was missed, and offered to exclude all subjects who missed the doses. An agreement was reached that in the sensitivity analyses the Applicant would exclude subjects who missed study medication during the timeframe of the shortage.

2.2 Data Sources

The electronic version of this BLA can be found at \\cbsap58\M\eCTD_Submissions\STN125289\125289.enx.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

C0524T05 (GO-BEFORE)

Study Design and Endpoints

Study C0524T05, also known as GO-BEFORE, was a double-blind, active-controlled study of golimumab in MTX-naïve patients with active rheumatoid arthritis. The study was conducted at 90 sites in multiple regions of the world; 18 sites were domestic. Six hundred thirty-seven (637) subjects were randomized into four groups in roughly equal proportions: injected placebo + MTX, golimumab 100 mg + oral placebo, golimumab 50 mg + MTX, golimumab 100 mg + MTX. A multiple-dummy design was used to ensure blindness.

Since this review only covers efficacy data received through week 24, the description of the design will focus on that time period. It should be noted, however, that the blinded, placebo-controlled portion of the study continued until week 52. In the period of the study now under consideration, a subject visited the site every four weeks and received a study injection (placebo or golimumab) at each visit. Oral treatment (placebo or MTX) was given weekly. Patients receiving MTX were given a starting dose of 10 mg, which was escalated to 20 mg by week 8.

The Clinical Study report lists two "co-primary" efficacy endpoints, the American College of Rheumatology (ACR) 50 response at Week 24 and another based on the Health Assessment Questionnaire (HAQ) at Week 52. The HAQ data were not provided in this submission, however. For present purposes, the ACR 50 response is the sole primary efficacy endpoint in the study. The ACR 50 is defined as follows:

1. An improvement of ≥ 50% from baseline in both the swollen joint count (66 joints) and tender joint count (68 joints), and

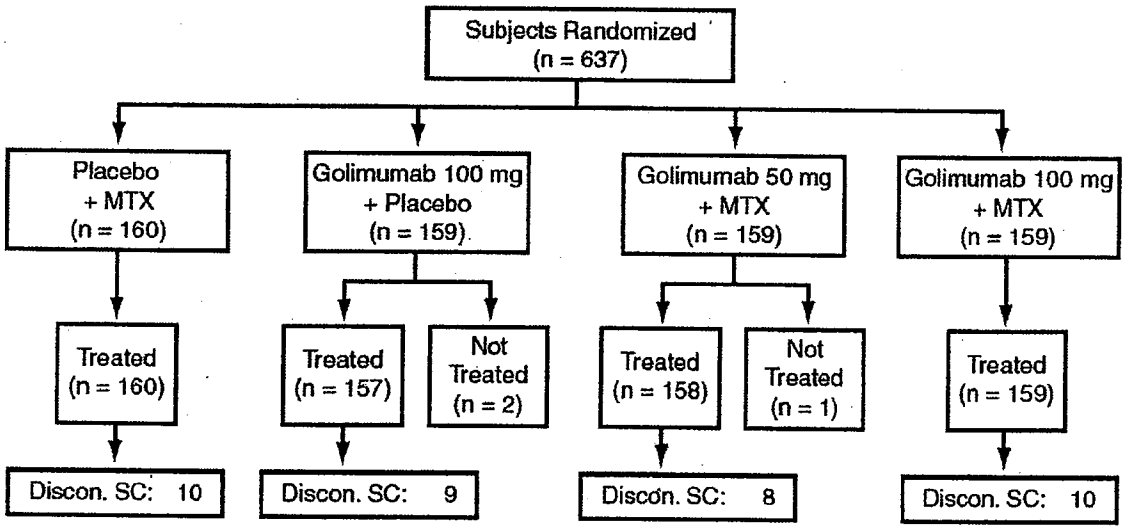
2. An improvement of ≥ 50% from baseline in at least 3 of the following 5 assessments:
   a) Patient's assessment of pain
   b) Patient's Global Assessment of Disease Activity
   c) Physician's Global Assessment of Disease Activity
   d) Patient's assessment of physical function as measured by the HAQ disability index,
   e) C-reactive protein (CRP)

Major secondary endpoints included the proportion of subjects achieving ACR 20 (20% improvement) at week 24 and proportion of subjects with abnormal CRP (> 1.0 mg/dL) at baseline who reached the primary endpoint.

Patient Disposition, Demographic and Baseline Characteristics

Figure 1 shows the disposition of the randomized subjects, including which subjects discontinued treatment with the subcutaneous (SC) study agent. It was provided by the Applicant but I verified the reported values. There was also a largely overlapping group of subjects who discontinued the oral study agent. Their treatment assignments were as follows: 12 in MTX-only (10 of whom discontinued SC), 10 in golimumab 100 mg-only (9 discontinued SC), 9 in golimumab 100 mg + MTX (8 discontinued SC), 10 in golimumab 100 mg + MTX (9 discontinued SC). Among the 37 patients who discontinued the SC study agent, the reasons were as follows: adverse event (13 patients), worsening of RA (1), unsatisfactory therapeutic effect (4), loss to follow-up (5), death (2), and "other" (12). Eleven of the 13 patients who discontinued SC treatment due to an adverse event were receiving golimumab + MTX. The breakdown of reasons among patients who discontinued oral treatment (largely the same patients) was similar.

Figure 1: Applicant's Disposition of Subjects through Week 24 (Source: Figure 2, CSR)



Discon. SC = Discontinuation of subcutaneous study agent.

Appears This Way
On Original

Table 2: Applicant's Demographic and Baseline Characteristics (Source: Table 12 in Clinical Study Report)

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX 50 mg	Golimumab + MTX 100 mg	Golimumab + MTX Combined	Total
Subjects randomized	160	159	159	159	318	637
Sex						
n	160	159	159	159	318	637
Male	26 (16.3%)	25 (15.7%)	24 (15.1%)	34 (21.4%)	58 (18.2%)	109 (17.1%)
Female	134 (83.8%)	134 (84.3%)	135 (84.9%)	125 (78.6%)	260 (81.8%)	528 (82.9%)
Race						
n	160	159	159	159	318	637
Caucasian	114 (71.3%)	111 (69.8%)	119 (74.8%)	117 (73.6%)	236 (74.2%)	461 (72.4%)
Black	6 (3.8%)	4 (2.5%)	1 (0.6%)	1 (0.6%)	2 (0.6%)	12 (1.9%)
Asian	25 (15.6%)	31 (19.5%)	30 (18.9%)	31 (19.5%)	61 (19.2%)	117 (18.4%)
Other	15 (9.4%)	13 (8.2%)	9 (5.7%)	10 (6.3%)	19 (6.0%)	47 (7.4%)
Age (yrs)						
n	160	159	159	159	318	637
Mean ± SD	48.6 ± 12.91	48.2 ± 12.85	50.9 ± 11.32	50.2 ± 11.87	50.6 ± 11.58	49.5 ± 12.28
Median	50.0	49.0	51.0	50.0	51.0	50.0
IQ range	(40.5, 57.0)	(39.0, 56.0)	(45.0, 58.0)	(41.0, 58.0)	(42.0, 58.0)	(41.0, 57.0)
Range	(19, 79)	(18, 85)	(21, 82)	(18, 82)	(18, 82)	(18, 85)
Weight (kg)						
n	160	158	158	159	317	635
Mean ± SD	71.61 ± 18.134	71.66 ± 21.044	73.30 ± 17.552	71.11 ± 17.463	72.20 ± 17.514	71.92 ± 18.577
Median	70.00	67.00	70.00	68.30	69.00	69.00
IQ range	(58.00, 81.40)	(58.00, 82.00)	(62.00, 83.00)	(59.40, 79.40)	(60.00, 80.50)	(59.40, 81.00)
Range	(40.0, 134.2)	(36.0, 167.8)	(35.8, 125.5)	(37.0, 135.0)	(35.8, 135.0)	(35.8, 167.8)
Height (cm)						
n	160	159	158	159	317	636
Mean ± SD	162.7 ± 8.84	162.1 ± 9.07	162.4 ± 9.02	163.0 ± 8.75	162.7 ± 8.88	162.6 ± 8.91
Median	163.0	161.4	162.5	162.6	162.6	162.0
IQ range	(156.0, 168.0)	(157.0, 167.0)	(156.0, 168.0)	(157.0, 168.0)	(156.0, 168.0)	(156.2, 168.0)
Range	(145, 193)	(139, 193)	(143, 200)	(146, 190)	(143, 200)	(139, 200)

RE2444P_DEM_1_AL 25OCT2007 15:57

Appears This Way
On Original

Table 2 shows the baseline characteristics of the randomized subjects. While it was provided by the Applicant, I verified all of the reported values except for the inter-quartile ranges. The subjects were largely female (83%) and Caucasian (72%). The imbalanced sex ratio is consistent with the population of RA patients (Peter E. Lipsky, Rheumatoid Arthritis, in *Harrison's Principles of Internal Medicine - 17th Ed.*, McGraw-Hill: New York, 2008).

Protocol Deviations

A substantial number of subjects either missed or had out-of-window administrations of either the injected or oral study agents. An unknown number of these incidents were related to a supply problem reported by the Applicant between October 2006 and February 2007. In a meeting on August 21, 2007, the Applicant stated that their records do not indicate which subjects missed a treatment during this time specifically because of the shortage.

Table 3: Applicant's Protocol Deviations in SC Agent Administration through Week 24 (Source: Table 8 in CSR)

		Golimumab	Golimumab + MTX			
	Placebo + MTX	100 mg + Placebo	50 mg	100 mg	Combined	Total
Subjects treated	160	157	158	159	317	634
Subjects with SC study agent administration deviation	23 (14.4%)	40 (25.5%)	24 (15.2%)	23 (14.5%)	47 (14.8%)	110 (17.4%)
Received incorrect study agent or dose	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.3%)	1 (0.2%)
Missed an administration	7 (4.4%)	13 (8.3%)	7 (4.4%)	6 (3.8%)	13 (4.1%)	33 (5.2%)
Received scheduled administration outside protocol-specified window	17 (10.6%)	31 (19.7%)	17 (10.8%)	16 (10.1%)	33 (10.4%)	81 (12.8%)

Table 3, which was provided by the Applicant, shows the number of treated subjects in each group who either missed a SC dose administration or were treated out-of-window. It also shows the small number of subjects who received the wrong agent or dose. The missed SC doses are not of concern in some sense, because they could only bias the results toward the null hypothesis. (This is discussed more in Section 5.1.) The out-of-window SC doses are only a concern insofar as they alter the interval between the primary endpoint and the previous SC treatment.

Table 4: Applicant's Protocol Deviations in Oral Agent Administration (Source: Table 10, CSR)

		Golimumab	Golimumab + MTX			
	Placebo + MTX	100 mg + Placebo	50 mg	100 mg	Combined	Total
Subjects treated	160	157	158	159	317	634
Subjects with oral study agent administration deviation	36 (22.5%)	59 (37.6%)	55 (34.8%)	57 (35.8%)	112 (35.3%)	207 (32.6%)
Received incorrect study agent or dose	21 (13.1%)	26 (16.6%)	22 (13.9%)	27 (17.0%)	49 (15.5%)	96 (15.1%)
Missed an administration	24 (15.0%)	42 (26.8%)	38 (24.1%)	37 (23.3%)	75 (23.7%)	141 (22.2%)

Table 4, also provided by the Applicant, shows the corresponding numbers for the oral study agent. Since the add-on MTX treatment was given orally, missed oral doses could bias the study

either toward retaining or rejecting the null hypothesis. As it happened, the control group (MTX-only) had the fewest missed doses in this study, so the net effect should be to bias toward the retaining the null hypothesis of no treatment effect.

Statistical Methods

The treatment randomization was stratified by screening CRP (< 1.5 mg/dL; >= 1.5 mg/dL) and site, using a biased coin method. This class of methods seeks to minimize the imbalance of treatment assignments across stratification factors by identifying the treatment assignment for a particular subject that would yield the best balance, then giving that treatment the highest probability of selection. In the Applicant's particular implementation, the measure of the balance resulting from a potential treatment assignment is the sum of three variances: the variance of the number of subjects in each treatment group within the site, within the stratum, and across the overall study. The treatment which would yield the best balance is chosen with probability .85, and the remaining probability of .15 is divided equally among the other treatments.

While biased coin randomization yields the desirable result of better balance, it can potentially invalidate the results of conventional statistical tests which assume completely random assignment. This problem and a solution are discussed more in section 5.

The primary endpoint, the proportion of subjects achieving an ACR 50 response at Week 24, was analyzed using a CMH test stratified by CRP at baseline (< 1.5 mg/dL, >= 1.5 mg/ML). The tests were two-sided at the .05 level. The analysis population was all randomized subjects, and they were analyzed according to the assigned treatment regardless of whether they received it (intent-to-treat). A sequential gatekeeping strategy was planned whereby the first comparison would be between the combined golimumab + MTX group (combining 50 mg and 100 mg doses) and the MTX-only group. If this test was significant, then the golimumab 50 mg + MTX group and the golimumab 100 mg + MTX group would be individually compared to the MTX-only group. If either if the two previous comparisons were significant, then a non-inferiority (NI) test was planned comparing the golimumab 100 mg-only group to the MTX-only group. A 95% confidence interval was to be used for NI with a margin of .1, a difference that the Applicant deemed not to be "clinically relevant".

The planned imputation method for the primary endpoint was as follows. If none of the components of the ACR 50 were observed at Week 24, then the subject would be deemed a non-responder. If at least one of the ACR components was observed at that time, then last-observation-carried forward (LOCF) imputation was to be used for the remaining components. If all observations were missing for a component, then 0% improvement was to be imputed for that component. If the baseline value was missing, then the median baseline value for the stratum would be imputed. Subjects were considered "treatment failures", and hence non-responders, if they did any of the following: initiated certain therapies (DMARDs, systemic immunosuppressives, biologics), discontinued study injections due to "unsatisfactory therapeutic effect", or received prohibited corticosteroid therapy.

Results and Conclusions

Table 5 shows the results for the primary efficacy analysis; it is taken from the Applicant but I replicated the results. Following the planned gatekeeping strategy, the comparison of the combined golimumab + MTX group with MTX alone was not quite significant at the pre-specified .05 level. When only the golimumab 50 mg + MTX group is compared with MTX, the resulting p-value was significant. Neither the golimumab 100 mg-only group nor the golimumab 100 mg + MTX group were statistically different from MTX.

Table 5: Applicant's Primary Endpoint - ACR 50 at Week 24, Randomized Subjects (Source: Table 17, CSR)

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX		
			50 mg	100 mg	Combined
Subjects randomized	160	159	159	159	318
ACR 50					
n	160	159	159	159	318
Subjects in response	47 (29.4%)	52 (32.7%)	64 (40.3%)	58 (36.5%)	122 (38.4%)
p-value		0.521	0.042	0.177	0.053
Subjects with CRP < 1.5 mg/dL at screening					
n	83	80	82	82	164
Subjects in response	21 (25.3%)	30 (37.5%)	33 (40.2%)	24 (29.3%)	57 (34.8%)
Subjects with CRP ≥ 1.5 mg/dL at screening					
n	77	79	77	77	154
Subjects in response	26 (33.8%)	22 (27.8%)	31 (40.3%)	34 (44.2%)	65 (42.2%)

The Applicant also ran a post-hoc analysis in which the analysis population consists of subjects that were not only randomized but actually received study treatment (modified ITT). Applying the stricter criterion removed two subjects from the golimumab 100 mg group and one subject from the golimumab 50 mg + MTX group. The results of the post-hoc analysis, which I also replicated, are shown in Table 6. Both the golimumab 50 mg + MTX group and the combined golimumab + MTX group were significantly different from placebo in this analysis.

The Applicant reported a number of sensitivity analyses, which are shown in Table 7. The results are fairly consistent insofar as they show a marginal-at-best effect of the golimumab 50 mg + MTX treatment, while the combined golimumab + MTX treatment specified for gatekeeping purposes is similarly marginal. Sensitivity analysis #2 is of particular interest as it is similar to baseline-observation-carried-forward (BOCF), which is generally accepted as a conservative imputation method that assigns a "bad" outcome to dropouts. An arguable flaw of analysis #2 is that it counts two subjects who withdrew due to an AE as responders. When these subjects are counted as non-responders, the response rates are as follows: 29.4% for MTX-only, 39.6% for golimumab 50 mg + MTX, 37.4% for combined golimumab + MTX.

Table 6: Applicant's ACR 50 at Week 24, Treated Subjects (Source: Attach. 3.5, CSR)

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX		
			50 mg	100 mg	Combined
Subjects treated	160	157	158	159	317
ACR 50					
n	160	157	158	159	317
Subjects in response	47 (29.4%)	52 (33.1%)	64 (40.5%)	58 (36.5%)	122 (38.5%)
p-value		0.473	0.038	0.177	0.049
Subjects with CRP < 1.5 mg/dL at screening					
n	83	80	82	82	164
Subjects in response	21 (25.3%)	30 (37.5%)	33 (40.2%)	24 (29.3%)	57 (34.8%)
Subjects with CRP ≥ 1.5 mg/dL at screening					
n	77	77	76	77	153
Subjects in response	26 (33.8%)	22 (28.6%)	31 (40.8%)	34 (44.2%)	65 (42.5%)

Table 7: Applicant's Sensitivity Analyses. Analysis method, percent response, p-value vs. MTX-only.

Sensitivity Analysis	MTX-only	Golim. 50 mg + MTX	Combin. Golim. + MTX
1. Non-responder if discontinue due to AE	29.4%	39.6% .055	37.7% .071
2. Non-responder if insufficient data to determine ACR 50	29.4%	40.3% .042	38.1% .061
3. "Observed data only"	31.1%	42.1% .046	39.9% .063
4. Exclude if missed >= 3 consecutive oral doses or 1 SC dose prior to week 24	30.5%	40.1% .082	39.0% .077
5. Non-responder if missed >= 3 consecutive oral doses or 1 SC dose prior to week 24	28.8%	37.1% .113	36.2% .106
6. Analysis 4, missed doses limited to supply shortage period.	30.3%	40.0% .076	38.5% .085
7. Analysis 5, missed doses limited to supply shortage period.	31.4%	39.0% .071	37.4% .082

Regarding the major secondary endpoints, both the golimumab 50 mg + MTX and the golimumab 100 mg + MTX groups were superior to MTX alone on the ACR 20 at Week 24. In both cases the response rate was (coincidentally) 62%, compared to 49% for MTX. Subjects with abnormal CRP showed numerical trends on the ACR 50 response at week 24 favoring both golimumab + MTX groups over MTX alone.

In summary, the primary and secondary endpoints provide some evidence that the golimumab 50 mg dose was effective in MTX-naïve subjects when used concomitantly with MTX in this trial. Since golimumab monotherapy is not indicated as an RA treatment in the proposed label, I did not evaluate the Applicant's claim that golimumab was non-inferior to MTX in this trial.

C0524T06 (GO-FORWARD)

Study Design and Endpoints

Study C0524T06, also known as GO-FORWARD, was a double-blind active-controlled study of golimumab in patients with active RA despite treatment with MTX. The study was conducted at 65 sites (60 of which enrolled subjects) throughout the world. In the study, 444 subjects were randomized to the following four treatment groups in a 3:3:2:2 ratio: injected placebo + MTX (n =133), golimumab 100 mg + oral placebo (n =133), golimumab 50 mg + MTX (n = 89), and golimumab 100 mg + MTX (n = 89). As with the GO-BEFORE study, a multiple-dummy design was used. Golimumab/placebo injections were given every four weeks, while the oral MTX/placebo was taken weekly. In contrast to the uniform dosing in the GO-BEFORE study, subjects in this study who received active MTX were given the stable weekly dose that they used at baseline (at least 15 mg/week).

The double-blind portion of the study lasted for 52 weeks, but the present NDA submission only includes data from the first 24 weeks. The protocol allowed for early escape at Week 16 for subjects who showed less than 20% improvement from baseline in both swollen and tender joint count. Subjects in the MTX-only group who qualified for early escape were switched to the golimumab 50 mg + MTX treatment. Subjects in either the golimumab-100mg-only group or the golimumab 50 mg + MTX group who qualified for early escape were switched to golimumab 100 mg + MTX treatment. The switching was done in a double-blind fashion.

The "co-primary" endpoints in this study were the proportion of subjects who had an ACR 20 response at Week 14 and the improvement from baseline in the health assessment questionnaire (HAQ) score at Week 24. The ACR 20 is similar to the ACR 50 (see page 11), but the criterion for improvement on a component is 20% instead of 50%. The HAQ (specifically the disability index) is a 20-question instrument in which patients are asked to rate the difficulty they have performing tasks in eight functional areas. Responses are scored from 0 (no difficulty) to 3 (inability to perform). The score for each functional area is the highest score for any question, with the exception that dependence on aids or devices raises the area score to at least 2 (i.e., scores of 0 or 1 are raised to 2). If an item is missing, then the area score is based on the other items. The HAQ score is the mean of the eight area scores.

There were also three major secondary endpoints included in this submission:

- Proportion of achieving at least moderate response on the Disease Activity Score (DAS) using C-reactive protein (CRP) at Week 14
- ACR 20 response at Week 24
- Improvement from baseline in HAQ at Week 14

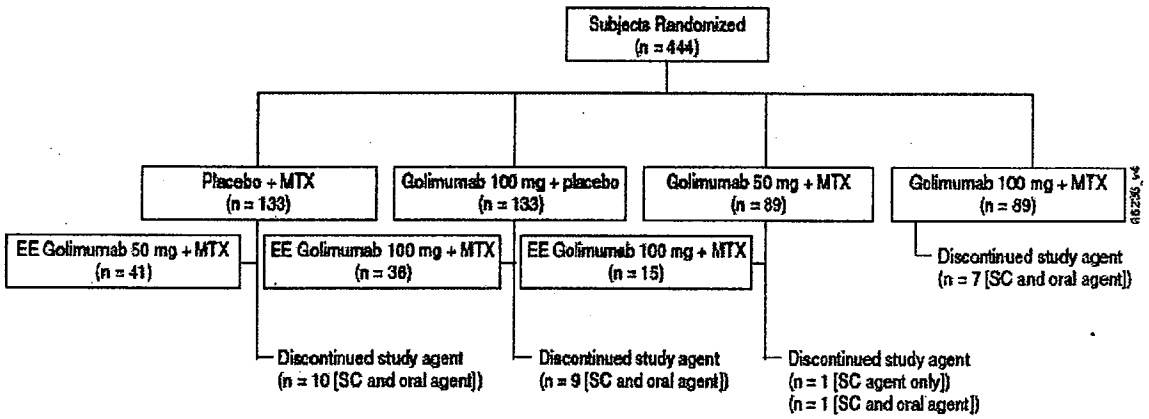
The van der Heijde Modified Sharp score at Week 24 was also pre-specified as a secondary endpoint, but was not submitted (perhaps because it is not needed for a signs and symptoms indication).

Patient Disposition, Demographic and Baseline Characteristics

Figure 2, which was provided by the Applicant, shows the disposition of the randomized subjects. I verified the values in the figure from the data file DISPOSIT, with one exception: DISPOSIT indicates that 42 patients in the placebo + MTX group qualified for early escape. According to the SUBJSF data set, there was one subject (5204-60124) in this group who qualified for early escape but was never exposed to the new treatment. Of the 28 patients who discontinued the SC study agent through week 24, 19 discontinued due to an AE.

Table 8 shows the baseline characteristics of the randomized subjects. While it was also provided by the Applicant, I verified all of the reported values except for the inter-quartile ranges. As in the previous study, the subjects were largely female (82%) and Caucasian (76%).

Figure 2: Applicant's Disposition of Subjects through Week 24 (Source: Figure 2, CSR)



Appears This Way
On Original

Table 8: Applicant's Baseline and Demographic Characteristics (Source: Table 7, CSR)

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX 50 mg	Golimumab + MTX 100 mg	Golimumab + MTX Combined	Total
Subjects randomized	133	133	89	89	178	444
Sex						
n	133	133	89	89	178	444
Male	24 (18.0%)	28 (21.1%)	17 (19.1%)	17 (19.1%)	34 (19.1%)	86 (19.4%)
Female	109 (82.0%)	105 (78.9%)	72 (80.9%)	72 (80.9%)	144 (80.9%)	358 (80.6%)
Race						
n	133	133	89	89	178	444
Caucasian	101 (75.9%)	104 (78.2%)	66 (74.2%)	70 (78.7%)	136 (76.4%)	341 (76.8%)
Black	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
Asian	21 (15.8%)	19 (14.3%)	15 (16.9%)	13 (14.6%)	28 (15.7%)	68 (15.3%)
Other	9 (6.8%)	8 (6.0%)	8 (9.0%)	6 (6.7%)	14 (7.9%)	31 (7.0%)
Age (yrs)						
n	133	133	89	89	178	444
Mean ± SD	51.2 ± 11.96	50.0 ± 11.47	50.3 ± 10.98	50.0 ± 10.78	50.2 ± 10.85	50.4 ± 11.36
Median	52.0	51.0	52.0	50.0	51.0	51.0
IQ range	(42.0, 58.0)	(42.0, 59.0)	(43.0, 57.0)	(45.0, 56.0)	(44.0, 57.0)	(43.0, 58.0)
Range	(27, 78)	(21, 74)	(18, 79)	(23, 76)	(18, 79)	(18, 79)

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX 50 mg	Golimumab + MTX 100 mg	Golimumab + MTX Combined	Total
Weight (kg)						
n	133	133	89	89	178	444
Mean ± SD	73.03 ± 18.902	74.18 ± 17.895	73.11 ± 17.793	70.44 ± 16.344	71.77 ± 17.088	72.87 ± 17.876
Median	70.00	71.70	72.00	68.00	70.00	70.15
IQ range	(58.00, 83.30)	(61.00, 84.10)	(60.00, 81.50)	(60.00, 79.00)	(60.00, 80.50)	(59.50, 82.05)
Range	(43.5, 127.8)	(42.0, 141.5)	(39.0, 146.0)	(40.0, 136.1)	(39.0, 146.0)	(39.0, 146.0)
Height (cm)						
n	133	133	89	89	178	444
Mean ± SD	163.7 ± 8.60	164.2 ± 9.56	164.3 ± 8.66	163.1 ± 10.28	163.7 ± 9.50	163.9 ± 9.24
Median	163.0	164.0	164.0	161.0	163.0	163.9
IQ range	(157.0, 170.0)	(157.5, 170.0)	(160.0, 169.0)	(156.0, 170.0)	(157.0, 170.0)	(157.0, 170.0)
Range	(149, 184)	(143, 189)	(143, 196)	(143, 194)	(143, 196)	(143, 196)

RE245:[P_DEM_1_A]. 17OCT2007 19:12

Protocol Deviations

As in study C0524T05, there were a substantial number of patients who either missed an SC treatment or, more commonly, took it out-of-window. Protocol deviations in SC agent administration through week 24 are broken down by treatment group in Table 9, which was provided by the Applicant.

Table 9: Applicant's Protocol Deviations in SC Agent Administration (Source: Table 6, CSR)

		Golimumab	Golimumab + MTX			
	Placebo + MTX	100 mg + Placebo	50 mg	100 mg	Combined	Total
Subjects treated	133	133	89	89	178	444
Subjects with SC study agent administration deviation	28 (21.1%)	38 (28.6%)	28 (31.5%)	26 (29.2%)	54 (30.3%)	120 (27.0%)
Received incorrect study agent or dose	0 (0.0%)	1 (0.8%)	1 (1.1%)	0 (0.0%)	1 (0.6%)	2 (0.5%)
Missed an administration	2 (1.5%)	5 (3.8%)	2 (2.2%)	3 (3.4%)	5 (2.8%)	12 (2.7%)
Received scheduled administration outside protocol-specified window	26 (19.5%)	34 (25.6%)	27 (30.3%)	23 (25.8%)	50 (28.1%)	110 (24.8%)

There were also a substantial number of patients who missed an oral dose or received the wrong dose/agent, as shown in Table 10. In this study the group with the fewest number of missed oral doses was golimumab 50 mg + MTX, so there is concern about a potential anti-conservative bias (i.e., against the null hypothesis) from the missed doses.

Table 10: Applicant's Deviations in Oral Agent Administration through Week 24 (Source: Attach. 1.15, CSR)

		Golimumab	Golimumab + MTX			
	Placebo + MTX	100 mg + Placebo	50 mg	100 mg	Combined	Total
Subjects treated	133	133	89	89	178	444
Subjects with oral study agent administration deviation	37 (27.8%)	47 (35.3%)	21 (23.6%)	27 (30.3%)	48 (27.0%)	132 (29.7%)
Received incorrect study agent or dose	12 (9.2%)	19 (14.3%)	11 (12.4%)	8 (9.0%)	19 (10.7%)	50 (11.3%)
Missed an administration	29 (22.0%)	34 (25.6%)	16 (18.0%)	24 (27.0%)	40 (22.5%)	103 (23.3%)

Statistical Methods

Randomization was stratified by site, using a biased coin randomization method similar to that used for study C0524T05. The implementation was slightly modified, however, so that the treatments could be assigned in a 3:3:2:2 ratio.

Pearson's chi-square test was used to compare the proportion of subjects responding to treatment, and in particular was used for the co-primary ACR 20 endpoint. "Continuous" endpoints, including the co-primary HAQ score, were analyzed using the van der Waerden normal scores test. The analysis population was all randomized subjects, and they were analyzed according to the assigned treatment (intent-to-treat).

A nested gatekeeping strategy was planned to maintain an overall type I error rate of .05. The two primary endpoints were to be tested in the following order: ACR 20 at Week 14, then improvement in HAQ at Week 24. Within these two endpoints, a gatekeeping strategy was also used to control multiplicity across doses. The first comparison was the combined golimumab + MTX group (both doses of golimumab) vs. MTX alone. If this test was significant, then the individual golimumab + MTX groups (golimumab 50 mg + MTX, golimumab 100 mg + MTX) were to each be compared with MTX alone. If either of these two tests was significant, then the golimumab 100 mg monotherapy group was to be compared to the MTX group. All tests were performed at a two-sided .05 level. It is not clear from the protocol or SAP exactly which results would be needed on the ACR 20 endpoint to move on to testing the HAQ.

Imputation for the ACR 20 endpoint was similar to that used for ACR 50 endpoint in C0524T05. Subjects were considered treatment failures (and non-responders) if they met any of failure criteria used in that study or if their dose of oral study agent was raised above baseline.

Imputation for the HAQ endpoint was as follows. If a subject was assigned to a different treatment because of early escape, then the score from Week 16 was imputed at Week 24. If there was missing data, then the method of imputation for the HAQ depended on whether a subject changed treatment due to early escape (i.e., subjects not in the golimumab 100 mg + MTX group who qualified for EE). The imputation rules for the EE subjects are described in the SAP (p. 27) as follows:

- If subjects do not have any data through Week 16, the improvement in HAQ at Week 24 will be imputed with the median score of all subjects [sic] improvement in HAQ at Week 16.
- 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 (including baseline).
- If baseline HAQ scores are missing, the baseline HAQ score will be imputed with median HAQ score based on all subjects' data at baseline.

Imputation for the non-EE subjects is described as follows:

- If subjects 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 subjects' data.
- 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 (including baseline).
- If baseline HAQ scores are missing, the baseline HAQ score will be imputed with median HAQ score based on all subjects' data at baseline.

This imputation plan is not ideal, as subjects who drop out due to adverse events could still have a good HAQ score carried forward. The Applicant also included a sensitivity analysis that uses observed data only.

Results and Conclusions

Table 11 shows the results for the ACR 20, Week 14 endpoint, which was one of the two primary endpoints. The table was provided by the Applicant, but I verified the results. The combined golimumab + MTX group was superior to MTX alone, as were the individual doses. Receiving golimumab and MTX together raised a patient's chance of response by an absolute amount of 22-23%, compared to receiving MTX alone. The golimumab-only group also did numerically better than MTX (by 11%), and was just outside of the .05 boundary for significance.

Table 11: Applicant's Co-Primary Endpoint - ACR 20 at Week 14 (Source: Table 13, CSR)

	Placebo + MTX	Golimumab 100 mg + Placebo	Golimumab + MTX		
			50 mg	100 mg	Combined
Subjects randomized	133	133	89	89	178
ACR 20					
n	133	133	89	89	178
Subjects in response	44 (33.1%)	59 (44.4%)	49 (55.1%)	50 (56.2%)	99 (55.6%)
p-value		0.059	0.001	< 0.001	< 0.001

The Applicant reported a number of sensitivity analyses which are shown in Table 12. The significant findings for the golimumab 50 mg + MTX group and as well the combined golimumab + MTX groups were found to be robust across the various analyses.

Table 12: Applicant's Sensitivity Analyses. Analysis method, percent response, p-value vs. MTX.

Sensitivity Analysis	MTX-only	Golim. 50 mg + MTX	Combin. Golim. + MTX
1. Non-responder if discontinue due to AE	33.1%	55.1% .001	55.6% <.001
2. Non-responder if insufficient data to determine ACR 20	33.1%	53.9% .002	55.1% <.001
3. "Observed data only"	34.1%	55.2% .002	56.3% <.001
4. Exclude if missed >= 3 consecutive oral doses	33.3% (n=132)	55.7% .001 (n=88)	55.5% <.001 (n=173)
5. Exclude if missed >= 3 consecutive oral doses or 1 SC dose prior to week 14	33.8%	57.0% <.001	56.1% <.001
6. Non-responder if missed >= 3 consecutive oral doses or 1 SC dose prior to week 14	33.1%	55.1% .001	53.9% <.001
7. Analysis 5, missed doses limited to supply shortage period.	33.8%	57.0% <.001	55.8% <.001
8. Analysis 6, missed doses limited to supply shortage period.	33.1%	55.1% .001	53.9% <.001

Table 13 shows the results for the other primary endpoint, improvement in the HAQ score at Week 24. I verified the Applicant's findings.

Table 13: Applicant's Co-Primary Endpoint -- Improvement in HAQ at Week 24 (Source: Table 14, CSR)

			Golimumab + MTX		
	Placebo + MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined
Subjects randomized	133	133	89	89	178
Improvement from baseline					
n	133	133	89	89	178
Mean ± SD	0.1316 ± 0.58374	0.2387 ± 0.66295	0.4663 ± 0.55255	0.4466 ± 0.51569	0.4565 ± 0.533
Median	0.1250	0.1250	0.3750	0.5000	0.4375
IQ range	(-0.1250, 0.3750)	(-0.2500, 0.6250)	(0.1250, 0.7500)	(0.1250, 0.7500)	(0.1250, 0.750
Range	(-1.375, 2.125)	(-1.375, 2.375)	(-0.750, 2.125)	(-1.000, 1.625)	(-1.000, 2.12
p-value		0.240	< 0.001	< 0.001	< 0.001

The only sensitivity analysis reported for the HAQ endpoint was an analysis using only observed data. The results of this analysis were consistent with those from the primary analysis, showing that the combination therapies are superior to MTX alone ($p < .001$ in both cases). Another set of analyses that I performed on the HAQ can be found in this section under "All Studies".

The results for the major secondary endpoints were supportive of a finding of efficacy for both golimumab doses in combination with MTX. The probability of a DAS28 response at Week 14 was significantly higher in both the golimumab 50 mg + MTX group (74.2%) and the golimumab 100 mg + MTX group (76.4%) compared the MTX-only group (51.9%). As Table 14 shows, the ACR 20 response at Week 24 was similar to that found at Week 14. Finally, the findings for the improvement in the HAQ score at Week 14 were similar to those at Week 24.

Table 14: Applicant's ACR 20 at Week 24 (Source: Table 16, CSR)

			Golimumab + MTX		
	Placebo + MTX	Golimumab 100 mg + Placebo	50 mg	100 mg	Combined
Subjects randomized	133	133	89	89	178
ACR 20					
n	133	133	89	89	178
Subjects in response	37 (27.8%)	47 (35.3%)	53 (59.6%)	53 (59.6%)	106 (59.6%)
p-value		0.187	< 0.001	< 0.001	< 0.001

In summary, this study supported a finding of efficacy for both golimumab doses in combination with MTX in MTX-experienced subjects.

C0524T11 (GO-AFTER)

Study Design and Endpoints

Study C0524T11, also known as GO-AFTER, was a double-blind, placebo-controlled study of golimumab in subjects with RA who had previously been treated with biologic anti-TNFα agent(s). The study was conducted at 101 sites (86 of which enrolled subjects) in North America, Europe, and Australia/New Zealand. Four hundred sixty-one subjects were randomized to the following treatments: placebo (n=155), golimumab 50 mg (n=152), and golimumab 100 mg (n=152). Golimumab/placebo injections were given every four weeks. It should be noted that this study ***did not test golimumab as a monotherapy***; subjects were allowed to stay on a variety of background therapies, including MTX. Sixty-six percent of subjects were taking MTX at baseline.

As with the GO-FORWARD study, this protocol allowed for early escape at Week 16 for subjects who showed less than 20% improvement from baseline in both swollen and tender joint count. Subjects in the placebo group who qualified for early escape were switched to golimumab 50 mg, and those in the 50 mg group were switched to 100 mg.

The primary endpoint was the proportion of patients achieving an ACR 20 response at Week 14. The following were specified as major secondary endpoints:

- ACR 50 response at Week 14
- DAS28 (using CRP) response at Week 14
- ACR 20 response at Week 24
- Improvement from baseline in HAQ score at Week 24

Patient Disposition, Demographic and Baseline Characteristics

Figure 3, which the Applicant provided and I verified, shows the disposition of the randomized subjects through week 24. As the figure shows, there were markedly more discontinuations in the placebo group (20%) than in the golimumab groups (8-9%). The most common reasons for discontinuation among all subjects were unsatisfactory therapeutic effect (4.8%), adverse event (3.5%), and "other" (3.5%).

Table 15 shows the baseline characteristics of the randomized subjects. While it was provided by the Applicant, I verified all of the reported values except for the inter-quartile range.

Figure 3: Applicant's Disposition of Subjects (Source: Figure 2, CSR)

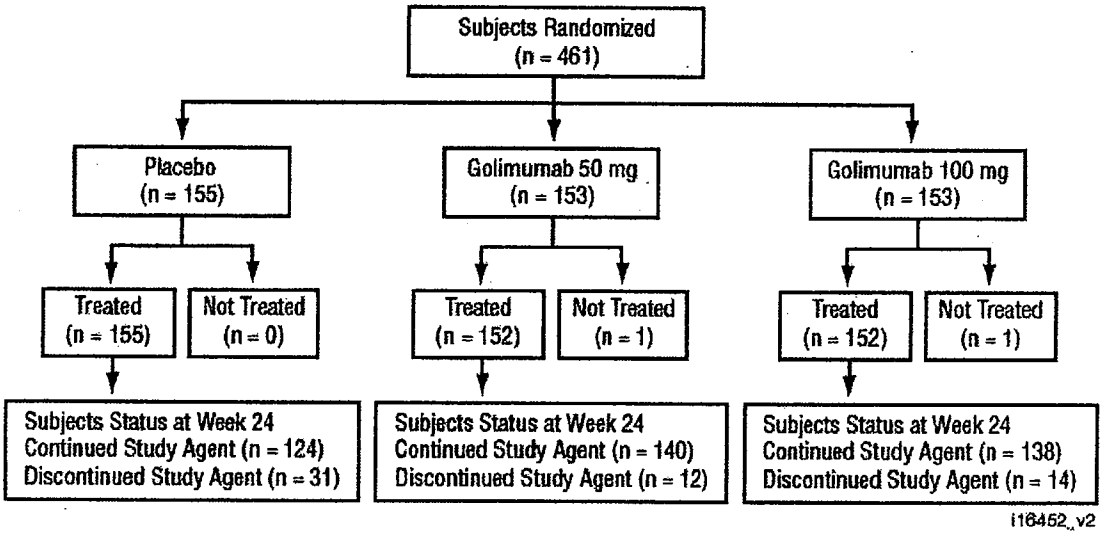


Table 15: Applicant's Baseline and Demographic Characteristics (Source: Table 9, CSR)

		Golimumab			
	Placebo	50 mg	100 mg	Combined	Total
Subjects randomized	155	153	153	306	461
Sex					
n	155	153	153	306	461
Male	23 (14.8%)	40 (26.1%)	31 (20.3%)	71 (23.2%)	94 (20.4%)
Female	132 (85.2%)	113 (73.9%)	122 (79.7%)	235 (76.8%)	367 (79.6%)
Race					
n	155	153	153	306	461
Caucasian	133 (85.8%)	135 (88.2%)	135 (88.2%)	270 (88.2%)	403 (87.4%)
Black	8 (5.2%)	10 (6.5%)	7 (4.6%)	17 (5.6%)	25 (5.4%)
Asian	2 (1.3%)	3 (2.0%)	3 (2.0%)	6 (2.0%)	8 (1.7%)
Other	12 (7.7%)	5 (3.3%)	8 (5.2%)	13 (4.2%)	25 (5.4%)
Age (yrs)					
n	155	153	153	306	461
Mean ± SD	54.8 ± 13.07	53.9 ± 11.47	53.7 ± 12.26	53.8 ± 11.85	54.1 ± 12.27
Median	54.0	55.0	55.0	55.0	54.0
IQ range	(46.0, 64.0)	(46.0, 63.0)	(47.0, 61.0)	(47.0, 62.0)	(46.0, 63.0)
Range	(26, 83)	(26, 75)	(23, 77)	(23, 77)	(23, 83)
Weight (kg)					
n	153	153	152	305	458
Mean ± SD	77.73 ± 20.765	81.02 ± 20.686	79.54 ± 20.197	80.28 ± 20.423	79.43 ± 20.551
Median	74.80	77.60	75.00	76.00	75.45
IQ range	(62.70, 86.40)	(66.50, 92.00)	(66.15, 90.40)	(66.30, 90.90)	(65.00, 90.00)
Range	(42.0, 160.8)	(45.0, 161.6)	(42.5, 146.0)	(42.5, 161.6)	(42.0, 161.6)
Height (cm)					
n	154	153	153	306	460
Mean ± SD	164.8 ± 8.44	165.9 ± 9.67	165.5 ± 9.20	165.7 ± 9.42	165.4 ± 9.11
Median	165.0	164.0	165.0	164.8	165.0
IQ range	(160.0, 170.0)	(159.0, 173.0)	(160.0, 172.0)	(159.0, 172.0)	(159.1, 171.8)
Range	(142, 191)	(145, 194)	(127, 189)	(127, 194)	(127, 194)

Protocol Deviations

As with the other studies, there were a number of patients who either missed an SC treatment or took it out-of-window. This is shown in Table 16. As noted earlier, missed SC doses could only introduce a bias in favor of the null hypothesis.

Table 16: Applicant's Protocol Deviations in Study Agent Administration through Week 24 (Source: Table 8, CSR)

		Golimumab			
	Placebo	50 mg	100 mg	Combined	Total
Subjects treated	155	152	152	304	459
Subjects with study agent administration deviation	52 (33.5%)	43 (28.3%)	54 (35.5%)	97 (31.9%)	149 (32.5%)
Received incorrect study agent or dose	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missed an administration	11 (7.1%)	11 (7.2%)	9 (5.9%)	20 (6.6%)	31 (6.8%)
Received scheduled administration outside protocol-specified window	46 (29.7%)	37 (24.3%)	47 (30.9%)	84 (27.6%)	130 (28.3%)

Statistical Methods

This study employed a biased coin randomization method similar to that used for study C0524T05. The randomization was stratified by site and baseline MTX use (yes/no).

The primary analysis was a CMH test stratified by baseline MTX use. The analysis population was all randomized subjects, and they were analyzed according to the assigned treatment (intent-to-treat). A gatekeeping strategy was planned whereby golimumab 100 mg was compared with placebo, then golimumab 50 mg was compared to placebo. Tests were two-sided at the .05 level. The planned imputation for the primary ACR 20 endpoint was the same as that used for the ACR 50 endpoint in the GO-BEFORE study. In addition to the treatment failure criteria outlined for that study, subjects would be classified as non-responders if they increased MTX, sulfasalazine, or hydroxychloroquine above the baseline dose for RA treatment.

Results and Conclusions

Table 17 shows the results for the primary endpoint, ACR 20 response at Week 14. Both doses of golimumab beat placebo (i.e., background) therapy. The table was provided by the Applicant but I verified the contents.

Table 17: Applicant's Primary Endpoint -- ACR 20 at Week 14 (Source: Table 16, CSR)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	155	153	153	306
ACR 20				
n	155	153	153	306
Subjects in response	28 (18.1%)	54 (35.3%)	58 (37.9%)	112 (36.6%)
p-value		< 0.001	< 0.001	< 0.001
Subjects receiving MTX at baseline				
n	107	103	102	205
Subjects in response	18 (16.8%)	41 (39.8%)	42 (41.2%)	83 (40.5%)
Subjects not receiving MTX at baseline				
n	48	50	51	101
Subjects in response	10 (20.8%)	13 (26.0%)	16 (31.4%)	29 (28.7%)

The Applicant conducted a series of sensitivity analyses that was quite similar to those reported for the GO-BEFORE study (Table 7). The only difference was that the number of missed oral doses was not considered. The results of these analyses, as reported by the Applicant, all support a finding of efficacy for both golimumab doses.

The results for the major secondary endpoints were supportive of the findings for the primary endpoint. The probability of an ACR50 response at week 14 was significantly higher in both the golimumab 50 mg group (16%) and the golimumab 100 mg group (20%) than in the placebo group (6%). Similarly, the proportion achieving an ACR 20 response at Week 24 was substantially higher in both the 50 mg group (34%) and the 100 mg group (44%) than in the placebo group (17%). The DAS28 response also showed a large treatment effect, with the active treatment groups showing a 56-60% chance of response compared to 30% in the placebo group. Finally, each of the golimumab groups showed a greater improvement in HAQ than the placebo group.

In summary, this study supported a finding of efficacy for both golimumab doses in combination with background therapy in anti-TNF-experienced subjects.

All Studies

At the request of Dr. Eric Brodsky, I performed a descriptive frequency analysis of subjects who showed a "clinically meaningful" improvement in their HAQ disability index at week 24. The standard criterion for a clinically meaningful improvement in the HAQ disability index at the population level is .22 or greater. Since the HAQ score is an average of eight whole numbers, however, it is always a multiple of .125. Hence on an individual level the cut-off score of .22 is equivalent to a cut-off of .25. In addition to the imputation that method used by the Applicant, I

also ran a more conservative analysis that classified patients who were treatment failures or discontinued the SC agent by week 24 as non-responders on the HAQ. The results, shown in Table 18, are consistent with the other efficacy findings. Both golimumab + MTX groups show a substantial advantage over the control treatment in studies C0524T06 and C0524T11. For the MTX-naïve patients in study C0524T05, all treatments showed a clinically meaningful improvement for a large proportion of the subjects.

Table 18: Clinically Meaningful (>= .25) Improvement on HAQ at Week 24

Study C0524T05				
	Treatment			
	MTX	**Golim. 100 mg**	**Golim. 50 mg + MTX**	**Golim. 100 mg + MTX**
Centocor Imput.	66%	65%	72%	78%
Conservative Imput.	63%	61%	68%	73%
Study C0524T06				
	Treatment			
	MTX	**Golim. 100 mg**	**Golim. 50 mg + MTX**	**Golim. 100 mg + MTX**
Centocor Imput.	38%	44%	67%	72%
Conservative Imput.	35%	42%	65%	64%
Study C0524T11				
	Treatment			
	Placebo	**Golim. 50 mg**	**Golim. 100 mg**	
Centocor Imput.	34%	50%	54%	
Conservative Imput.	28%	44%	49%	

3.2 Evaluation of Safety

The safety profile of golimumab was reviewed by Eric Brodsky, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Tables 19-21 show the results for the primary endpoints of the three studies by sex. The ITT analysis set was used. The large imbalance in favor of female patients precludes meaningful inferential analysis, but no distinct pattern is apparent across studies.

Table 19: Study C0524T05, ACR 50 at Week 24 by Sex

Sex	Treatment	N	[illegible]
Female	MTX	134	25%
	Golimumab 100 mg	134	33%
	Golimumab 50 mg + MTX	135	36%
	Golimumab 100 mg + MTX	125	35%
Male	MTX	26	50%
	Golimumab 100 mg	25	32%
	Golimumab 50 mg + MTX	24	63%
	Golimumab 100 mg + MTX	34	41%

Table 20: Study C0524T06, ACR 20 at Week 14 by Sex

Sex	Treatment	N	[illegible]
Female	MTX	109	35%
	Golimumab 100 mg	105	45%
	Golimumab 50 mg + MTX	72	54%
	Golimumab 100 mg + MTX	72	57%
Male	MTX	24	25%
	Golimumab 100 mg	28	43%
	Golimumab 50 mg + MTX	17	59%
	Golimumab 100 mg + MTX	17	53%

Table 21: Study C0524T11, ACR 20 at Week 14 by Sex

Sex	Treatment	N	[illegible]
Female	Placebo	132	17%
	Golimumab 50 mg	113	31%
	Golimumab 100 mg	122	38%
Male	Placebo	23	22%
	Golimumab 50 mg	40	48%
	Golimumab 100 mg	31	39%

Tables 22-24 show the primary outcomes by race. The preponderance of Caucasian patients precludes meaningful inferential analysis.

Table 22: Study C0524T05, ACR 50 at Week 24 by Race

Race	Treatment	N	Prop.
Asian	MTX	25	20%
	Golimumab 100 mg	31	26%
	Golimumab 50 mg + MTX	30	30%
	Golimumab 100 mg + MTX	31	26%
Black	MTX	6	50%
	Golimumab 100 mg	4	25%
	Golimumab 50 mg + MTX	1	0%
	Golimumab 100 mg + MTX	1	100%
Caucasian	MTX	114	30%
	Golimumab 100 mg	111	36%
	Golimumab 50 mg + MTX	119	44%
	Golimumab 100 mg + MTX	117	36%
Other	MTX	15	33%
	Golimumab 100 mg	13	23%
	Golimumab 50 mg + MTX	9	33%
	Golimumab 100 mg + MTX	10	70%

Table 23: Study C0524T06, ACR 20 at Week 14 by Race

Race	Treatment	N	Prop.
Asian	MTX	21	33%
	Golimumab 100 mg	19	63%
	Golimumab 50 mg + MTX	15	60%
	Golimumab 100 mg + MTX	13	69%
Black	MTX	2	50%
	Golimumab 100 mg	2	0%
Caucasian	MTX	101	33%
	Golimumab 100 mg	104	42%
	Golimumab 50 mg + MTX	66	56%
	Golimumab 100 mg + MTX	70	53%
Other	MTX	9	33%
	Golimumab 100 mg	8	38%
	Golimumab 50 mg + MTX	8	38%
	Golimumab 100 mg + MTX	6	67%

Table 24: Study C0524T11, ACR 20 at Week 14 by Race

Race	Treatment	N	Rate
Asian	Placebo	2	0%
	Golimumab 50 mg	3	33%
	Golimumab 100 mg	3	33%
Black	Placebo	8	50%
	Golimumab 50 mg	10	20%
	Golimumab 100 mg	7	29%
Caucasian	Placebo	133	17%
	Golimumab 50 mg	135	38%
	Golimumab 100 mg	135	39%
Other	Placebo	12	17%
	Golimumab 50 mg	5	0%
	Golimumab 100 mg	8	38%

Tables 25-27 show the primary outcomes by age group. For each study, I used logistic regression to test for an interaction between age group and treatment. Analyses were done both with and without the age-65-and-over subgroup (due to its small size). All treatment levels were included. Baseline CRP was included as a factor in the analysis for study C0524T05, and baseline MTX was included for study C0524T11. None of the three studies showed a significant interaction.

Table 25: Study C0524T05, ACR 50 at Week 24 by Age

Age	Treatment	N	Rate
< 45	MTX	58	29%
	Golimumab 100 mg	58	40%
	Golimumab 50 mg + MTX	39	49%
	Golimumab 100 mg + MTX	50	42%
>= 45 and < 65	MTX	87	29%
	Golimumab 100 mg	84	31%
	Golimumab 50 mg + MTX	106	38%
	Golimumab 100 mg + MTX	91	35%
>= 65	MTX	15	33%
	Golimumab 100 mg	17	18%
	Golimumab 50 mg + MTX	14	36%
	Golimumab 100 mg + MTX	18	28%

Table 26: Study C0524T06, ACR 20 at Week 14 by Age

Age	Treatment	[illegible]	[illegible]
< 45	MTX	40	40%
	Golimumab 100 mg	40	50%
	Golimumab 50 mg + MTX	26	58%
	Golimumab 100 mg + MTX	21	48%
>= 45 and < 65	MTX	75	25%
	Golimumab 100 mg	82	45%
	Golimumab 50 mg + MTX	54	50%
	Golimumab 100 mg + MTX	62	60%
>= 65	MTX	18	50%
	Golimumab 100 mg	11	18%
	Golimumab 50 mg + MTX	9	78%
	Golimumab 100 mg + MTX	6	50%

Table 27: Study C0524T11, ACR 20 at Week 14 by Age

Age	Treatment	[illegible]	[illegible]
< 45	Placebo	31	19%
	Golimumab 50 mg	36	33%
	Golimumab 100 mg	32	53%
>= 45 and < 65	Placebo	86	20%
	Golimumab 50 mg	86	40%
	Golimumab 100 mg	93	39%
>= 65	Placebo	38	13%
	Golimumab 50 mg	31	26%
	Golimumab 100 mg	28	18%

4.2 Other Special/Subgroup Populations

Since the Applicant does not propose to use weight-based dosing for golimumab, I performed an exploratory analysis of the relationship between body weight and the effect of treatment. In studies C0524T06 and C0524T11 there was some evidence that golimumab was less effective for heavier subjects. Notably, however, there was no indication that the 100 mg dose was more effective for these subjects than the 50 mg dose. I shared my findings with the rest of the review team.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This application is supported by three Phase 3 trials, two of which had highly significant efficacy results for the proposed 50 mg dose and a third which had marginal results. The interpretation of these trials is somewhat complicated, however, by irregularities in drug administration which were related to an unknown degree to a supply shortage which affected both oral and injected treatments.

In the case of the injected agent (golimumab or placebo), subjects who miss a dose are not a cause for concern from the standpoint of evaluating the Applicant's claim of efficacy. Missing an injection should tend to bias the results toward supporting the null hypothesis. If a subject misses an injection of golimumab, then he or she is losing both the biological effect of the agent as well as the placebo effect of injection. If a placebo injection is missed, on the other hand, then only the placebo effect is lost. Hence, the only way missed injections could bias the results ***away*** from the null hypothesis is if there were a strong placebo effect (relative to the biological effect) and the missed injections were overwhelmingly found in the control group. In fact, none of the three studies had an imbalance of that sort, as seen in Tables 3, 9, and 16.

In the case of missed oral treatments, a bias away from the null hypothesis results if there are more missed doses of MTX (i.e., less MTX exposure) in the control group than in the golimumab + MTX treatment groups. In study C0524T05 the MTX-only group had the lowest rate of missed oral doses. In C0524T06 the MTX-only group had a slightly higher rate than the golimumab 50 mg + MTX group (20% vs. 18%) and a lower rate than the golimumab 100 mg + MTX group. The number of missed doses of MTX was not reported for study C0524T11, perhaps because it was considered a "background therapy".

Following the reasoning in the previous paragraphs, it is unlikely in principle that the missed treatments had a net effect of making golimumab appear more efficacious than it actually is. It is reassuring, furthermore, that the planned sensitivity analyses were quite supportive of the primary efficacy analysis in two of the studies (C0524T06 and C0524T11). In study C0524T05 the results did not undermine the marginal finding of efficacy.

The possibility of missed oral doses biasing the results of C0524T11 cannot be ruled out, as the relevant data were not provided for this study. It is unlikely that the MTX supply problem adversely affected different treatment groups, however, based on the following reasoning: Treatment was randomly assigned, with stratification by site. Shortages of MTX would equally affect all subjects on MTX background therapy at a given site. Hence the relationship between treatment and missed MTX therapy should be random.

In addition to the incidents of missed doses, the Applicant also reported that a number of injected doses were given out-of-window. After discussion with Eric Brodsky, M.D., I concluded that since golimumab works over a relatively long time scale it is unlikely that these deviations would have biased the efficacy analysis.

Aside from effects of the missed or out-of-window doses themselves, an additional potential concern from the supply shortage is the possibility of investigators becoming unblinded based on their ability to dispense medication to a given patient. In response to an information request, Centocor stated the following:

> • Blinded inventory was controlled through an Interactive Voice Response System (IVRS).
> • At each visit, investigators dispensed study medication to an individual subject by identifying, from their inventory, the specific blinded carton containing the unique carton number provided by the IVRS.
> • The IVRS was prospectively designed such that if a particular drug type was not available at a site at the time of randomization, forced randomization was not permitted. An individual subject's treatment group could not be inferred based on the inability of the IVRS to dispense study medication.

Based on these assurances, I conclude that the investigators were not unblinded.

A final complication of the pivotal studies is that the Applicant used biased coin randomization. As noted earlier, this type of randomization somewhat undermines the basis of the conventional statistical tests because it makes a particular subject's treatment assignment dependent on the assignments made to previous subjects. One solution to this problem is to conduct a re-randomization test. Using this approach, subjects retain their original outcomes but are randomly assigned new treatments using the same randomization algorithm that was used in the original study. In particular, the original order of entry is used when making the new random assignments. The randomization is replicated many times (e.g., 10,000) and the null distribution of the test statistic is estimated. Comparing the actual test statistic to the null distribution then yields a valid p-value. In response to an information request, the Applicant conducted such tests for the primary endpoint of study C0524T11 and the results were similar to those obtained from the original tests.

The usual re-randomization test, as described above, could not be used for studies C0524T05 and C0524T06. The reason is that these studies had an extra golimumab-only arm that is not relevant to the comparison of golimumab + MTX to MTX alone. Under a complete re-randomization, subjects who received golimumab alone would have often been assigned to the other arms, simulating a different null hypothesis (i.e., all study treatments are interchangeable with respect to the outcome) than the one of interest (i.e., all study treatments ***that include MTX*** are interchangeable).

To get around this problem, the Applicant used a novel ***weighted re-randomization*** method proposed by [redacted] Under this method, the randomization was forced so that subjects originally assigned to golimumab monotherapy kept that assignment in each replication. Weights were then used to compute a p-value that is purported to be valid despite the forced randomization. This method appears adequate for the present purpose, and the results for the primary ACR endpoints in studies C0524T05 and C0524T06 were largely consistent with those from the original tests. In fact, the weight re-randomization tests tended to yield smaller p-values. (The only exception was the comparison of golimumab 100 mg + MTX to MTX alone in study C0524T05.)

b(4)

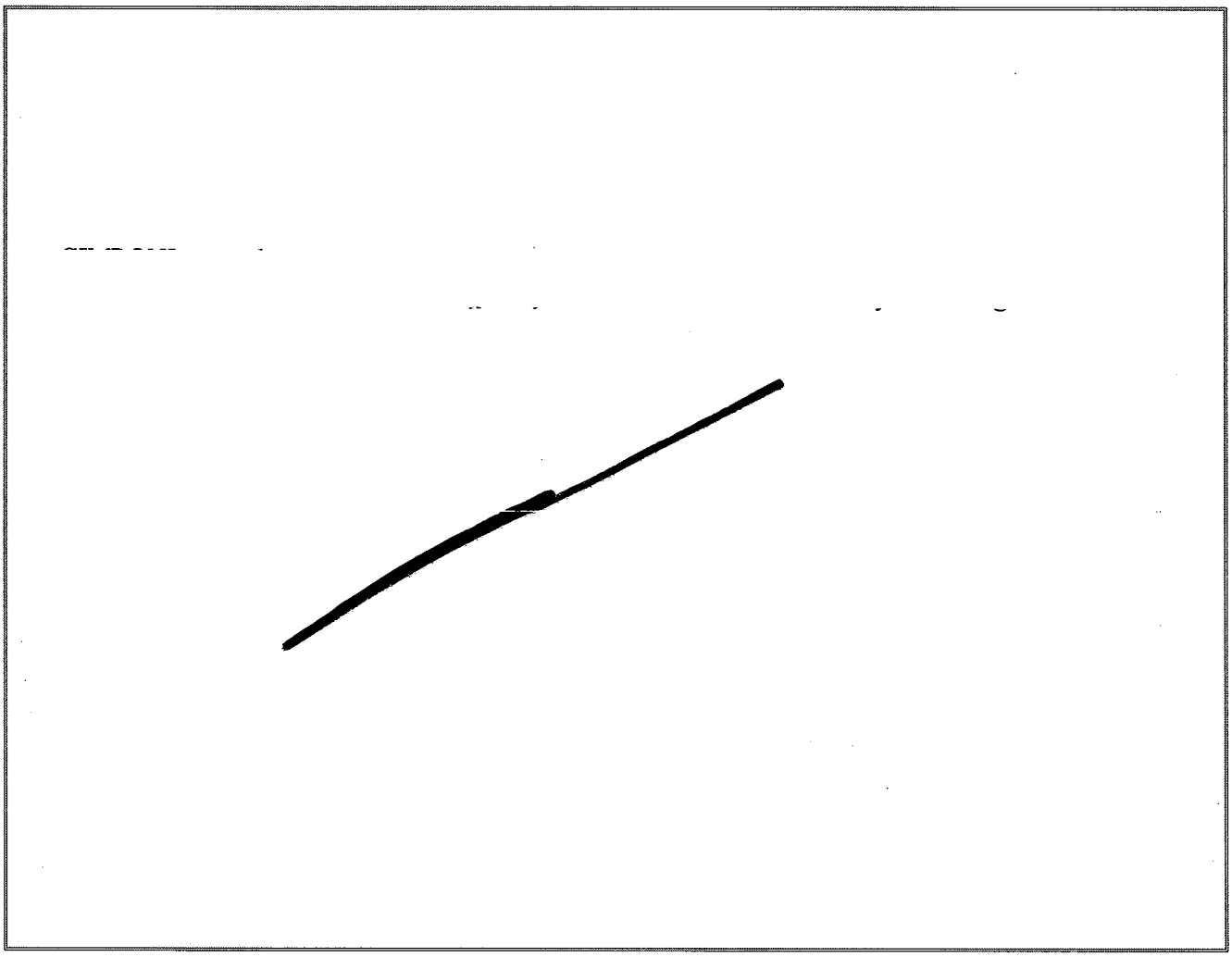
Although the Applicant proposes to market only the 50 mg dose of golimumab, there was some evidence that the 100 mg dose is also effective when used concomitantly with MTX. The two studies in MTX-experienced subjects showed significant effects of treatment.

5.2 Conclusions and Recommendations

The Applicant presented three studies of the efficacy of golimumab in treating signs and symptoms of rheumatoid arthritis, each in somewhat different patient populations. I find that the totality of the evidence indicates that the 50 mg dose of golimumab is effective for reducing signs and symptoms of RA when used in combination with methotrexate.

5.3 Review of the Proposed Label

Selections from the Applicant's proposed label language are shown in *italics*, and my comments are shown in regular type. Note that any references to figures and tables use different numbering than the rest of the report.



b(4)

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Statistical- 8

SIGNATURE LIST

Jonathan Norton, Primary Statistical Reviewer:

Jonathan Norton

Date: 2/27/2009

Dionne Price, Statistical Team Leader:

Dionne Price 3/4/09

Thomas Permutt, Biometrics Division Director:

Thomas Permutt 3/4/09