CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125289

STATISTICAL REVIEW(S)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

BLA:	125289/SN000
Name of drug:	SIMPONI (golimumab) for subcutaneous injection
Indication:	treatment of rheumatoid arthritis, psoriatic arthritis, and ankolysing spondylitis
Applicant:	Centocor
Dates:	Letter June 24, 2008; PDUFA April 24, 2009
Review priority:	S
Biometrics division:	Division of Biometrics II
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Keywords: NDA review, clinical studies

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The Applicant, Centocor Incorporated, seeks to market SIMPONI for the treatment of adult subjects (18 years or older) with active rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The proposed indication is:

SIMPONI, is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1) in combination with methotrexate:
  [redacted] adult subjects with moderate to severely active rheumatoid arthritis. [redacted]
- Psoriatic Arthritis (PsA) (1.2) alone or in combination with methotrexate: b(4)
  [redacted] active arthritis in adult subjects with psoriatic arthritis.
- Ankylosing Spondylitis (AS) (1.3):
  [redacted] adult subjects with active disease.

The focus of this statistical review is on the Psoriatric Arthritis and the Ankolysing Spondylitis studies. Dr. Jonathan Norton is the primary statistical reviewer for the Rheumatoid Arthritis studies.

Based on evidence from Studies C0524T08 (PsA) and C0524T09 (AS), golimumab 50 mg and golimumab 100 mg are effective in reducing signs and symptoms of PsA and AS.

Although no formal analysis was conducted to compare the golimumab dose groups, numerically, there is generally no difference in the proportion of responders (ACR 20 or ASAS 20) between golimumab 50 mg and golimumab 100 mg at Week 14. However at Week 24, a slightly higher proportion of ACR 20 responders and ASAS 20 responders in the golimumab 100 mg group were observed compared to golimumab 50 mg. In conclusion since there was no added benefit of golimumab 100 mg at Week 14, I agree with the Applicant's recommendation that patient should be administered golimumab 50 mg QD every four weeks.

Based on the analysis of Week 24 responders, there is evidence that most subjects receiving golimumab 50 mg or golimumab 100 mg achieved the level of response as early as Week 4 in both PsA and AS studies. Thirty percent of subjects in the PsA study and more than 50% of subjects in the AS study maintained their response at all visits (starting at Week 4). Therefore, there is evidence that subjects taking golimumab 50 mg QD every four weeks maintained their responder status throughout the treatment period.

Secondary endpoints were also analyzed. Although the results from the analyses of these endpoints are in favor of golimumab over placebo, I recommend that the results from the analyses of the endpoints that are not related to the indication (e.g. PASI 75 in the PsA) and those that do not provide additional information of benefit to clinicians (e.g. BASDAI in the AS study) be excluded in the label.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The clinical development program for SIMPONI (golimumab) includes data from five Phase 3 studies in subjects with the following chronic inflammatory disorders: RA (three studies), PsA (one study) and AS (one study). All five studies were multicenter, randomized, double-blind, and placebo-controlled. Both efficacy and safety of SIMPONI are based on 24-week data.

The PsA study (C0524T08) evaluated 405 subjects with active PsA despite current or previous disease-modifying antirheumatic drug (DMARD) or NSAID therapy, who had not been previously treated with anti-TNF therapy. The AS study (C0524T09) evaluated 356 subjects with active AS despite current or previous DMARD or NSAID therapy, who had not been previously treated with anti-TNF therapy.

1.3 STATISTICAL ISSUES AND FINDINGS

During my review of the PsA and AS studies, I found no issues that that could not be resolved by recoding and/or re-analyzing the data. An example is the randomization strategy (i.e. minimization with biased coin assignment) the Applicant applied to allocate patients. This approach seeks to determine treatment assignment of a new patient to minimize covariate imbalances between treatment groups. This is done by assigning the patient to the dose with the least overall imbalance with probability 0.89. However, this strategy may result in predictability of randomization sequences and may potentially undermine the applicability of conventional statistical tests (e.g. Cochran-Mantel Haenszel test).

The Applicant addressed the concern by conducting re-randomization tests for both studies. For each study, the Applicant generated 10,000 randomization sequences according to the randomization specification of the trial. For each randomization sequence, test statistics (combined golimumab group vs. placebo; golimumab 50 mg vs. placebo; golimumab 100 mg vs. placebo) were calculated based on the simulated treatment assignments. The results obtained by these tests were similar to the ones obtained by using the conventional CMH test.

In addition, although various discrepancies between the raw and derived datasets were observed, all of these discrepancies were found not to affect the overall conclusion.

Table 1 presents the results of the primary endpoint analyses for Study C0524T08 (PsA study) and Study C0524T09 (AS study). The results support the Applicant's proposed indication of [redacted] adult subjects with active PsA or with active AS. b(4)

The following is a summary of the results.

In Study C0524T08, there is evidence that golimumab 50 mg and golimumab 100 mg administered SC every four (q4) weeks in subjects with active PsA and who had not previously been treated with anti-TNF therapy reduces signs and symptoms of PsA. This is based on the result from the analysis of the primary endpoint (i.e. ACR 20 at Week 14). In addition, the proportions of subjects achieving an ACR 20 response in the golimumab groups were generally similar regardless of MTX use at baseline. However, a greater proportion of subjects in the placebo group receiving MTX versus those not receiving MTX achieved an ACR 20 response. The evidence is also supported by the results from the analyses of other endpoints (e.g. ACR 50, ACR70, ACRn index of improvement, and all ACR components), as well as result from the analysis of the ACR 20 at Week 24.

In Study C0524T09, there is evidence that golimumab 50 mg and golimumab 100 mg administered SC every four (q4) weeks in subjects with active AS (despite current or previous DMARD or NSAID therapy and had not been treated previously with anti-TNFα therapy) reduces signs and symptoms of AS. This is based on the result from the analysis of the primary endpoint (i.e. ASAS 20 at Week 14). The evidence is also supported by the results from the analyses of other endpoints (e.g. ASAS 40 and all the ASAS components), as well as result from the analysis of the ASAS 20 at Week 24.

The ASAS 20 response was slightly higher for each golimumab dose group in the higher CRP stratum compared to the lower CRP stratum. There is also a slightly higher response in the golimumab 100 mg compared to golimumab 50 mg in the lower CRP stratum, while a slightly lower response in the golimumab 100 mg compared to golimumab 50 mg in the higher stratum.

Table 1: Number of subjects (%) who achieved an ACR 20 response (Study C0524T08) and an ASAS 20 response (Study C0524T09) at Week 14

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Study C0524T08 Subjects Randomized	113	146	146	292
ACR 20 (Primary)	9 (8%)	74 (51%) <0.0001	66 (45%) <0.0001	140 (48%) <0.0001
MTX* at Baseline	55	71	71	142
ACR 20	7 (13%)	38 (54%)	32 (45%)	70 (49%)
Non-MTX at Baseline	58	75	75	150
ACR 20	2 (3%)	36 (48%)	34 (45%)	70 (47%)
Study C0524T09 Subjects Randomized	78	138	140	278
ASAS 20 (Primary)	17 (22%)	82 (59%) <0.0001	84 (60%) <0.0001	166 (60%) <0.0001
CRP ≤1.5 mg/dL* at screening	53	88	91	179
ASAS 20	12 (13%)	44 (50%)	49 (54%)	93 (52%)
CRP >1.5 mg/dL at screening	25	49	48	97
ASAS 20	5 (20%)	37 (76%)	34 (71%)	71 (73%)

*Breslow-Day test of homogeneity across MTX strata was not significant (i.e. no interaction).

2 INTRODUCTION

2.1 OVERVIEW

The Applicant, Centocor Incorporated, seeks to market SIMPONI for the treatment of adult subjects (18 years or older) with active rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The proposed indication is:

SIMPONI, is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA) (1.1) in combination with methotrexate: [redacted] adult subjects with moderate to severely active rheumatoid arthritis. [redacted]
- Psoriatic Arthritis (PsA) (1.2) alone or in combination with methotrexate: [redacted] active arthritis in adult subjects with psoriatic arthritis.
- Ankylosing Spondylitis (AS) (1.3): [redacted] adult subjects with active disease.

b(4)

The recommended dose for all three indications is golimumab 50 mg given monthly, [redacted] as a subcutaneous (SC) injection in a single-use autoinjector or single-use pre-filled syringe. In addition, SIMPONI is recommended in combination with methotrexate (MTX) in RA subjects, alone or in combination with MTX in PsA subjects and as monotherapy in AS subjects.

b(4)

The clinical development program includes data from five Phase 3 studies in subjects with the following chronic inflammatory disorders: RA (3 studies), PsA (1 study) and AS (1 study). All five studies were multicenter, randomized, double-blind, and placebo-controlled. Both efficacy and safety of SIMPONI are based on 24-week data.

The three Phase 3 RA studies evaluated 1542 subjects from three different subpopulations of subjects with moderate to severely active RA:

- C0524T06 (N=444): Subjects with active RA despite MTX treatment and no prior treatment with an anti-TNF agent
- C0524T11 (N=461): Subjects with active RA previously treated with 1 or more anti-TNF agents
- C0524T05 (N=637): Subjects with active RA naïve to MTX and no prior treatment with an anti-TNF agent

The PsA study (C0524T08) evaluated 405 subjects with active PsA despite current or previous disease-modifying antirheumatic drug (DMARD) or NSAID therapy, who had not been previously treated with anti-TNF therapy. The AS study (C0524T09) evaluated 356 subjects with active AS despite current or previous DMARD or NSAID therapy, who had not been previously treated with anti-TNF therapy.

The development plan for SIMPONI (golimumab) was introduced to the Division of Clinical Trial Design and Analysis of the Center for Biologics Evaluation and Research under BBIND9925. Following the reorganization of the therapeutic areas in the Center for Drug Evaluation and Research, golimumab fell under the purview of the Division of Review Management and Policy in 2004 before falling under the purview of the Division of Anesthesia, Analgesia and Rheumatology Products in

2006. The key milestones in the clinical development program are highlighted in Dr. Brodsky's review. This includes key interactions with the Agency from May 14, 2001 through August 29, 2007. Statistical issues were discussed during several meetings and key issues are summarized below:

1. Type C Teleconference Meeting (March 25, 2004)

The review division required 6-month data for each indication (RA, PsA, or AS). The review division also recommended enrolling subjects with all subtypes of PsA into the PsA trials, and enrolling subjects with AS associated with psoriasis or inflammatory bowel disease to better capture a representative sample of the PsA and AS populations, respectively, and to make the results more generalizable.

2. Type B (End of Phase 2) Meeting (April 6, 2005) – Discussion on Rheumatoid Arthritis

Protocol C0524T05:

- The review division accepted ACR50 measured at Week 24 as the primary endpoint to support an indication [redacted] The review division also suggested, as an alternative to ACR50 as the primary endpoint, using ordinal ACR scores as a primary endpoint, whereby subjects achieving <ACR 20, ≥ACR 20 to <ACR50, ≥ACR50 to <ACR70, and ≥ACR70 would be analyzed to better capture whether a clinically significant effect is obtained with golimumab. b(4)

- The review division would not require a statistically significant improvement in the proportion of subjects achieving an ACR 20 at Week 24.

- The review division agreed that the change from baseline in van der Heijde Sharp score (vdH-S) measured at Week 52 and change from baseline in Health Assessment Questionnaire (HAQ) measured at Week 52 (and at week 104) would be sufficient to evaluate the inhibition of the progression of structural damage and for a claim of improving physical function, respectively. The review division also suggests performing appropriate secondary analysis (i.e. comparing the proportion of subjects achieving an improvement in HAQ ≥0.3 units) to support a clinically significant effect.

- For subjects entering early escape, the analysis of the inhibition of structural damage at Week 52 will use a linear extrapolation method using vdH-S scores from baseline and Week 28, and for the analysis of physical function, a last observation carried forward approach will be employed. The review division also suggested applying appropriate sensitivity analysis using different imputation techniques.

- The review division agreed in principle with the approach that to define a 'major clinical response', subjects must maintain their ACR70 response for at least 6 consecutive months. The review division also stated that in order to determine whether to include [redacted] will be made after reviewing the relevant clinical information. b(4)

- The Applicant agreed to add a monotherapy arm to this study.

Protocol C0524T06:

- The review division agreed in principle that the primary endpoint is ACR 20 response measured at Week 14, and the major secondary endpoint is ACR 20 measured at Week 24. Subjects who entered early escape at Week 16 will be considered ACR 20 non-responder for the analysis of the secondary endpoint.

- The review division noted that in order for a monotherapy claim, the Applicant must show evidence by performing an additional study designed to demonstrate efficacy of monotherapy (pre-specification and winning), as well as to examine immunogenicity data to determine the incidence of anti-golimumab antibodies in the absence of a concomitant DMARD.

The Applicant proposed to use an adaptive stratified randomization method in both RA trials.

In terms of primary endpoint analysis, although the review division recommended that a claim be made only based on comparison between each individual dose group versus placebo and not on the combined comparison, the Applicant maintained that they will claim success only if the combined (golimumab doses) group and at least one golimumab dose group is significant compared to placebo. However, the Applicant will also consider using alternative approaches such as closed testing procedure for controlling the inflation of type 1 error rate.

3. Type B (Pre-IND Teleconference) Meeting (April 19, 2005) – Discussion on Ankolysing Spondylitis

   - The review division agreed that the primary endpoint (i.e. proportion of subjects achieving ASAS 20 at Week 14) and the secondary endpoints (i.e. proportion of subjects achieving ASAS 20 at Week 24, change from baseline in the radiographic progression (mSASSS) compared with a historical control at Week 104, the change from baseline in BASFI at Week 14, and the change from baseline in BASMI at Week 14) are appropriate [redacted] b(4)

   - [redacted] b(4)

   - Like the RA studies, the Applicant proposed to use an adaptive stratified randomization method in this study.

   - Like the RA studies, although the review division recommended that a claim on the primary endpoint be made only based on comparison between each individual dose group versus placebo and not on the combined comparison, the Applicant maintained that they will claim success only if the combined (golimumab doses) group and at least one golimumab dose group is significant compared to placebo. However, the Applicant will also consider using alternative approaches such as closed testing procedure for controlling the inflation of type 1 error rate.

4. Type B (Pre-IND Teleconference) Meeting (March 21, 2005) – Discussion on Psoriatic Arthritis

   - The review division agreed that the two co-primary endpoints (i.e. proportion of subjects with an ACR 20 response at Week 14 and the change from baseline in total radiographic scores of the hands and feet at Week 24), tested sequentially, are appropriate condition that radiographic effects observed at Week 24 are maintained to Week 52. The review division also agreed with the secondary endpoints (i.e. proportion of subjects with an ACR 20 response at Week 24, proportion of subjects with $\geq$75% improvement in Psoriasis Area Severity Index (PASI) at Week 14 and change from baseline in HAQ measured at Week 24 and maintenance benefit assessed at Week 104) are appropriate condition that physical function (i.e. measured by HAQ) is maintained through two years. In addition, the review division noted that the proportion of subjects achieving Psoriatic Arthritis Response criteria (PsARC) at Week 14 should not be considered a 'major secondary endpoint' since ACR 20 is accepted as an outcome measure for PsA.

   - The review division agreed that subjects entering early escape at Week 16 are considered non-responders for ACR 20 at Week 24. The review division expressed concern about the validity of linear extrapolation of radiographic data from Week 16 to Week 24 for subjects who entered early escape. The Applicant proposed to perform x-rays on all subjects at Week 24, regardless of early escape. The review division agreed to this approach but caution the Applicant of the risk of possibly underestimating the treatment effect.

   - [redacted] b(4)

   - Like the RA studies, the Applicant proposed to use an adaptive stratified randomization method in this study.

   - Like the RA studies, although the review division recommended that a claim on the primary endpoint be made only based on comparison between each individual dose group versus placebo and not on the combined comparison, the Applicant maintained that they will claim success only if

the combined (golimumab doses) group and at least one golimumab dose group is significant compared to placebo. However, the Applicant will also consider using alternative approaches such as closed testing procedure for controlling the inflation of type 1 error rate.

5. Protocol Reviews (September 26 to November 29, 2005)

The following were comments and recommendations provided to the Sponsor.

1. **The protocol entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab a Fully Human Anti-TNF α Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Rheumatoid Arthritis and Previously Treated with Biologic Anti-TNFα Agent(s)" has been reviewed. As discussed with you in the meeting on September 13, 2005 and during the teleconference of January 19, 2006, because of limitations in the current study design the results could not be used to support** b(4)
2. **The protocol entitled "Study C0524T05-A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in MTX-naïve Subjects with Active Rheumatoid Arthritis" has been reviewed. In the protocol, you stated that "A last observation carried forward (LOCF) procedure will be used to impute the missing ACR components if subjects have data for at least 1 ACR component at Week 24." Explain under what circumstance(s) the patients would have only one ACR component at Week 24 and the rest missing. Explain the utility of applying LOCF procedure to impute the missing ACR components compared to assigning the subject as a nonresponder.**
3. **In protocol C0524T05, the analysis of inhibition of structural damage at Week 52 will use a linear extrapolation method using vdH-S scores from baseline and Week 28 for the subjects who entered early escape. In Protocol C5024T06, the analysis of the physical function at Week 24 will use an LOCF method for missing HAQ scores. As stated in the meeting held March 8, 2005, additional appropriate sensitivity analysis exploring the use of different imputation techniques should be performed.**

6. Pre-BLA Meeting (August 21, 2007)

- In one of the RA study (C0524T05), the review division agreed with the 10% non-inferiority margin with some clarifications to the Applicant (e.g. what the Applicant referred to as positive test results for the 'analysis' meant, whether it is one-sided or two-sided test). The review division expressed that "success of the non-inferiority comparison could support efficacy of golimumab monotherapy. b(4)

- The review division recommended that in order to assess the efficacy of golimumab as monotherapy for the treatment of PsA, the Applicant should submit efficacy subgroup analyses based on concomitant MTX use for the three study arms.

- In terms of subgroup analyses by race, the review division recommended that the Applicant follow the classification use in the 2005 Collection of Race and Ethnicity Data in Clinical Trials Guidance. In terms of subgroup analyses by weight, the review division commented that if there is a marked difference between weight quartiles, that a more detailed analysis (e.g. using deciles) may be warranted.

- The review division has the following advice on the impact of study agent supply shortage.
  - In the two RA studies, the Applicant should perform sensitivity analyses on the primary endpoints by excluding subjects who missed ≥ 3 weekly oral doses of MTX or missed ≥ 1 SC dose of golimumab during the timeframe of the MTX and golimumab shortage (i.e. November 2006 to February 2007).
  - In the RA study with prior anti-TNF treatment, the PsA study and the AS study, the Applicant should perform sensitivity analyses on the primary endpoints by excluding subjects who missed ≥ 1 SC dose of golimumab during the timeframe of the MTX and golimumab shortage (i.e. November 2006 to February 2007).
  - In addition to the above, the Applicant should perform sensitivity analysis on all five Phase 3 studies by classifying subjects who missed ≥ 3 weekly oral doses of MTX or

missed ≥1 SC dose of golimumab as non-responders for the primary efficacy endpoint during the timeframe of the MTX and golimumab shortage (i.e. November 2006 to February 2007).

- Furthermore, the Applicant should provide counts of all subjects who missed any study treatments due to shortage, by study and treatment group and how many administrations were missed. The Applicant should also provide datasets identifying subjects who missed any administrations due to the shortage and how many were missed, and indicate missing data points due to the shortage.

The focus of this statistical review is on the Psoriatric Arthritis and the Ankolysing Spondylitis studies. Dr. Jonathan Norton is the primary statistical reviewer on the Rheumatoid Arthritis studies.

2.2 DATA SOURCES

This statistical review is based on data submitted in studies C0524T08 (Psoriatric Arthritis) and C0524T09 (Ankolysing Spondylitis).

The electronic submission of this BLA can be found at:
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3 STATISTICAL EVALUATION

Statistical evaluation of the PsA study will be discussed first followed by the AS study.

3.1 EVALUATION OF EFFICACY

3.1.1 PSORIATRIC ARTHRITIS

3.1.1.1 Study Design and Analysis Plan

C0524T08 is the only Phase 3 study conducted by the Applicant to evaluate the efficacy and safety of golimumab in subjects with active PsA. The efficacy is evaluated by assessing reduction in signs and symptoms of PsA and inhibition of progression of structural damage. Subjects eligible for this study were men and women with a diagnosis of PsA for at least 6 months prior to first study agent administration and who had active PsA despite current or previous DMARD or NSAID therapy, and who had not previously been treated with anti-TNFα therapy.

Study C0524T08 is currently ongoing and in this submission, the Applicant reported up to 24 weeks of data (placebo-controlled portion); therefore, inhibition of progression of structural damage will be addressed in a later report. Of note, all subjects were treated for at least 24 weeks or until they discontinued study agent or participation in the study.

The following is a brief summary of the study design.

C0524T08 has 3 distinct periods (Figure 1):

- Placebo-controlled period (Weeks 0 through 24), including Early Escape at Week 16
- Blinded active treatment period (Weeks 24 through 52), beginning with the crossover of placebo subjects to golimumab 50 mg at Week 24
- Long-term extension period (Weeks 52 through 268), beginning with the Week 52 study agent injection

The study was to be conducted at approximately 90 global investigational sites. Approximately 396 subjects were to be randomly assigned in a 1:1.3:1.3 ratio to 1 of 3 treatment groups: placebo, golimumab 50 mg or golimumab 100 mg. Treatment allocation will be by randomization via a centralized, interactive voice response system (IVRS) provided by [redacted] b(4)

In order to ensure relatively even treatment balance within sites, within baseline MTX usage (yes/no), and within the study overall, subject allocation to a treatment group was performed using an adaptive stratified randomization design. The randomization method is minimization with biased-coin assignment. The treatment-balancing algorithm will utilize approximately 90 sites and baseline MTX usage (2 levels: Yes, No). The measure used to calculate lack of balance in the minimization algorithm is the Variance. Weights for the balancing factors are Site (1), Screening MTX level (1), Overall Study (1). The probability of assignment to each treatment group based on the group with the lowest total imbalance measure is described in Table 2 below. Note that the algorithm seeks to maintain balance only at the individual factor margins and not at the cross-classification cell levels. Thus, treatment balance within every stratum formed by the cross-classification of the balancing factors is not expected. A carton number will be assigned based on subject's treatment assignment.

At Week 16, subjects in any group who had <10% improvement from baseline in both swollen and tender joint count qualified to enter early escape in a double-blinded fashion. Treatment for subjects who entered early escape was as follows:

Placebo → golimumab 50 mg SC injections at Weeks 16 and 20
Golimumab 50 mg → golimumab 100 mg SC injections at Weeks 16 and 20
Golimumab 100 mg → No change (golimumab 100 mg SC injections at Weeks 16 and 20)

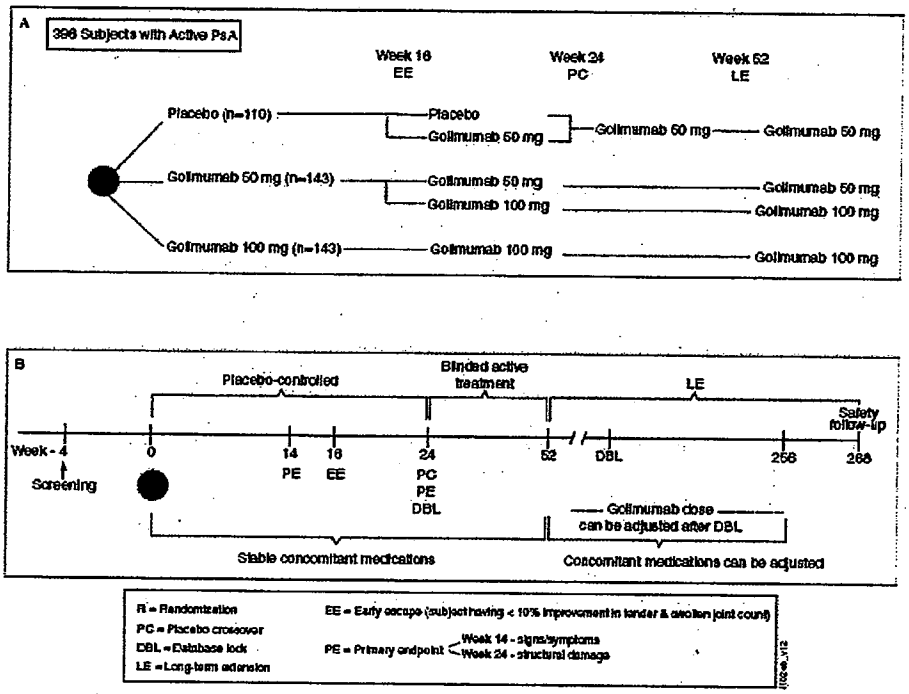
The IVRS will be used to qualify subjects for early escape. For the subjects who meet the early escape criteria, the carton number allocation will be based on their randomized treatment assignment and the corresponding changes associated with the treatment type due to early escape. For the subjects who do not meet the early escape criteria, the carton number allocation will continue to be of the treatment type based on their randomized treatment group.

As stated, the Applicant applied minimization with biased-coin assignment to allocate patients to a treatment group. This approach seeks to determine treatment assignment of a new patient to minimize covariate imbalances between treatment groups. This is done by assigning the patient to the dose with the least overall imbalance with probability 0.89 (see Table 2).

This strategy may result in predictability of randomization sequences and maypotentially undermine the applicability of conventional statistical tests (e.g. Cochran-Mantel Haenszel test).

An alternative approach is to use a re-randomization test, which is a simple nonparametric alternative. This approach requires no assumption than that of randomization. Under the null hypothesis of no treatment effect, the responses should be a deterministic sequence unaffected by the treatment assigned. Therefore, the distribution of the test statistic under the null hypothesis is computed with reference to all possible sequences of treatment assignments under the randomization procedure.

Figure 1: Study Design – C0524T08



Note: Panel A shows study treatments; Panel B shows key timepoints during the study.

Source: Clinical Study Report, page 29

Table 2: Assignment Probability for Adaptive Stratified Randomization Scheme

	Probability of Acceptance		
Group with Lowest Total Imbalance Measure	Group I (Placebo)	Group II (Golimumab 50 mg)	Group III (Golimumab 100 mg)
Group I	0.870	0.065	0.065
Group II	0.05	0.885	0.065
Group III	0.05	0.065	0.885

Source: Statistical Analysis Plan (Appendix 11 of CSR), page 22

On February 2, 2009 the Division requested the Applicant conduct re-randomization tests for the primary endpoints of the pivotal studies for BLA 125289 which includes studies C0524T08 and C0524T09).

- Replicate the randomization exactly with new random numbers
- Perform 10,000 replications for each study and compare primary test statistic(s) from the study to the empirical distribution(s) computed from the replications
- Provide algorithm, results and software code

On February 13, 2009, the Applicant responded and provided the Division with the results of re-randomization test for studies C0524T08 and C0524T09, along with the randomization specifications,

re-randomization algorithm and programs, and associated datasets. For each study, the following algorithm was used to generate the empirical distribution of the test statistics and to calculate the Monte Carlo p value.

1. Obtain the exact order of all randomization entries
2. 10,000 randomization sequences were generated according to the randomization specification of the trial, with the fixed order of subject entry.
3. The test statistics (combined golimumab group vs. placebo; golimumab 50 mg vs. placebo; golimumab 100 mg vs. placebo) were then calculated based on the simulated treatment assignment for each generated randomization sequence.
4. The Monte Carlo p value can be computed as the proportion of randomization sequences that have a test statistics greater than or equal to the observed test statistics, i.e.,

$$\hat{p} = \frac{\sum_{i=1}^{10000} I(T_i \geq T_{obs})}{10000}$$

where T_i is the test statistics based on i^{th} simulated randomization sequence, and T_{obs} is the test statistic based on the observed data.

The results from the re-randomization test are as follow (Table 3). Of note, the re-randomization test p-values in the table show the consistency of the results with those obtained by using the conventional CMH test when adaptive randomization was used.

Table 3: Results from Re-randomization Test

Study	Treatment group comparison	Observed p value	Re-randomization p value
C0524T08	Combined golimumab vs. placebo	<0.00001	0.0000
	Golimumab 50 mg vs. placebo	<0.00001	0.0000
	Golimumab 100 mg vs. placebo	<0.00001	0.0000
C0524T09	Combined golimumab vs. placebo	<0.00001	0.0000
	Golimumab 50 mg vs. placebo	<0.00001	0.0000
	Golimumab 100 mg vs. placebo	<0.00001	0.0000

There are two primary endpoints in this study that are referred to as coprimary endpoints by the Applicant. The coprimary endpoints are the proportion of subjects achieving an American College of Rheumatology (ACR) 20 response at Week 14 (i.e. to evaluate reduction in signs and symptoms of arthritis) and change from baseline in the PsA modified van der Heijde-Sharp (vdH-S) score at Week 24 (a radiographic indicator of disease progression). According to the Applicant,

ACR 20 response was chosen as a coprimary endpoint based on the clinical similarity of PsA and RA and the wide acceptance of ACR 20 by the rheumatology community and regulatory authorities as a measure of improvement in the signs and symptoms of the arthritic component of PsA. An ACR 20 response was defined as a ≥ 20% improvement from baseline in:

1. Swollen joint count (66 joints) and tender joint count (68 joints)

AND

2. 20% improvement from baseline in 3 of the following 5 assessments:

a. Subject's assessment of pain on a 0 to 10 cm VAS scale (no pain to the worst possible pain)
b. Subject's global assessment of disease activity on a 0 to 10 cm VAS scale (very well to very poor)
c. Physician's global assessment of disease activity on a 0 to 10 cm VAS scale (no active arthritis to extremely active arthritis)
d. Subject's assessment of physical function as measured by the HAQ on a scale of 0 to 3 (without any difficulty to unable to do)
e. CRP

Data for change from baseline in PsA modified vdH-S score at Week 24 (i.e. radiographic endpoint) will be presented in a later report, after all subjects have completed 52 weeks of treatment and imaging.

Reduction in signs and symptoms of arthritis was evaluated by comparing the proportion of subjects with ACR 20 response at Week 14 between the combined golimumab group (golimumab 50 mg and 100 mg groups combined) and the placebo group. A Cochran-Mantel-Haenszel (CMH) test with stratification by subjects' baseline MTX usage (yes/no) was performed for this analysis at a significance level of $\alpha = 0.05$. If this test was significant, pairwise comparisons between the golimumab 50 mg and placebo groups and between the golimumab 100 mg and placebo groups were performed using the same statistical procedure at a significance level of $\alpha = 0.05$ each.

Of note, analyses for Week 14 were not affected by early escape rules; the rules were applied for Week 24 efficacy analyses. The early escape rules are as follows:

> According to the Protocol, for subjects randomized to placebo who qualified for early escape, treatment was changed from placebo to golimumab 50 mg starting at Week 16. For subjects randomized to golimumab 50 mg and qualifying for early escape, treatment was changed from golimumab 50 mg to 100 mg starting at Week 16. Therefore, according to early escape rules, these subjects had their last observation prior to change in treatment carried forward for Week 24 analyses. Since subjects randomized to golimumab 100 mg who qualified for early escape remained on the 100 mg dose, their observed values at Week 24 were used for Week 24 analyses.

The following is a summary of the data handling rules:

> **Treatment Failure Rules**
>
> Treatment failure rules were applied in the primary analysis. These rules superseded the actual clinical response status value (yes/no) based on the ACR 20. Subjects were considered to have not achieved an ACR 20 response at Week 14 if, prior to Week 14, they:
>
> - Initiated any DMARDs, biologics, systemic immunosuppressives for PsA or increased MTX dose above baseline level for PsA.
> - Initiated treatment with oral, IV, or IM corticosteroids for PsA, or increased the dose of oral corticosteroids for PsA above baseline dose.
> - Discontinued study agent injections due to unsatisfactory therapeutic effect.
>
> **Missing Data Rules**
>
> Subjects with missing data for all of the ACR components at Week 14, were considered as ACR 20 nonresponders at Week 14. If subjects had data for at least 1 ACR component at Week 14, the following rules were applied:
>
> - Percent improvement from baseline at Week 14 was imputed as 0% for any ACR component, if the component values were missing from baseline through Week 14.
> - Any missing ACR component value at Week 14 was replaced by the last nonmissing observation (including baseline).

- Any missing baseline ACR component value (needed for computing percent improvement from baseline) was imputed as the median value of that component from all subjects with baseline data in the same stratum (baseline MTX use yes/no).

Three sensitivity analyses were performed by the Applicant and they are the following:

- The first sensitivity analysis was performed as a more conservative assessment of efficacy. This sensitivity analysis was performed using the treatment failure, joint evaluability (see Applicant's SAP, Section 7.1.1.1), adjusted joint count (see Applicant's SAP, Section 7.1.1.1), and missing data imputation rules. In addition, subjects who discontinued study treatment because of an AE prior to Week 14 (subjects expected to be more likely to have been receiving golimumab) were also considered to have not achieved an ACR 20 response at Week 14.

- The second sensitivity analysis was performed using the treatment failure, joint evaluability, and adjusted joint count rules and using actual observations, with no imputation for missing data. If the coprimary endpoint could not be determined due to insufficient data, then the subject was considered to have not achieved an ACR 20 response at Week 14.

- The third sensitivity analysis was performed using the treatment failure rules and using actual observations with no imputation for missing data. If the coprimary endpoint could not be determined due to insufficient data, then the subject was excluded.

The 'major' secondary efficacy endpoints the Applicant evaluated are:

1. ACR 20 response at Week 24 assesses whether subjects achieved sustained arthritis response. For subjects who met early escape criteria at Week 16 in the placebo and golimumab 50 mg groups, each ACR component value at Week 24 was to be replaced with the corresponding component value at Week 16.

2. Psoriasis Area and Severity Index (PASI) 75 improvement at Week 14 in a subset of subjects with ≥ 3% body surface area (BSA) psoriasis skin involvement at baseline. Of note, PASI 75 assesses the effect of golimumab therapy on psoriasis. PASI 75 is a dichotomous endpoint (whether or not a subject achieves ≥ 75% improvement from baseline in PASI score). A reduction in PASI score is an improvement. If any of the components required for computing the PASI score were missing, the PASI score was to be set to missing.

3. Improvement from baseline in the Health Assessment Questionnaire (HAQ) score at Week 24 assesses the functional status of a subject by means of the 20-questionnaire disability index of the HAQ. The disability index, which is a continuous outcome, is calculated as the sum of computed component scores divided by the number of categories answered. The disability index is not computed if the subject does not have scores for at least 6 categories.

4. Physical component summary score of the SF-36 at Week 14 which measures the disease burden in terms of physical functioning/improvement in quality of life.

In the analysis of secondary efficacy endpoints,

Pearson's chi-square test was used to compare binary categorical data, and the Cochran-Mantel-Haenszel (CMH) chi-square test to compare binary categorical data with stratification (stratified by baseline MTX usage [yes/no]). Analysis of variance (ANOVA) on van der Waerden normal scores with treatment and subject's baseline MTX usage as factors in the model was used to compare continuous data, unless otherwise specified.
The first test compared golimumab at any dose (golimumab 50 mg and 100 mg combined) versus placebo. If the results were significant, then pairwise comparisons of golimumab 50 mg versus placebo and golimumab 100 mg versus placebo were made. This method protected the significance level at 0.05: a golimumab dose group that was nominally significantly better than the placebo group would not be reported as significant unless the combined golimumab groups were significantly better than the placebo group as well. All statistical testing was 2-tailed, at a significance level of 0.05. In addition to statistical

analyses and tabulated descriptive statistics, graphical data displays (eg, box plots) and subject listings were also used to summarize/present the data.

Of note,

The results of these analyses were to be considered significant only if positive test result for the coprimary endpoint were achieved. For all these comparisons, the first test was to compare the combined golimumab group with placebo. If the results were significant, then pairwise comparisons of golimumab 50 mg versus placebo and golimumab 100 mg versus placebo were made.

3.1.1.2 Results and Discussion

3.1.1.2.1 Study Population and Demographic/Baseline Characteristics

A total of 405 subjects from 58 sites were randomly assigned to treatment (Table 4). Of the 405 subjects, 230 (57%) were in North America and 175 (43%) in Europe.

A total of 20 subjects discontinued study agent prior to Week 14, and only five additional subjects discontinued between Week 14 to Week 24, for a total of 25 subjects. A numerically greater proportion of placebo subjects discontinued study agent through week 14 (and through week 24) compared to the golimumab groups. Of the 25 subjects who discontinued study agent, 18 subjects terminated study participation. See Appendix 1 for definition of 'discontinued study agent'.

At Week 16 (early escape), 51 (45%) subjects in the placebo group began receiving golimumab 50 mg and 28 (19%) subjects randomized to golimumab 50 mg began receiving golimumab 100 mg. A minor discrepancy was observed upon re-analysis of the data using the early escape rule. Fifty two placebo subjects should enter early escape and switch to golimumab 50 instead of 51, and 27 subjects in golimumab 50 mg should switch to golimumab 100 mg instead of 28.

Of the 79 subjects who entered early escape at Week 16, only one subject in the placebo group discontinued study treatment through Week 24.

Table 4: Summary of Study Participating Status – Study C0524T08

		Golimumab	
	Placebo	50 mg	100 mg
Subjects Randomized	113	146	146
Subjects Treated	113	146	146
Discontinued study agent through Week 14	10 (9%)	7 (5%)	3 (2%) †
Adverse Event	4 (4%)	2 (1%)	3 (2%) †
Unsatisfactory therapeutic effect	2 (2%)	1 (1%)	0
Lost to follow-up	1 (1%)	1 (1%)	0
Other	3 (3%)	3 (2%)	0
Discontinued study agent through Week 24	12 (11%)	9 (6%)	4 (3%)
Adverse Event	5 (4%)	2 (1%)	4 (3%)
Unsatisfactory therapeutic effect	3 (3%)	1 (1%)	0
Lost to follow-up	1 (1%)	1 (1%)	0
Other	3 (3%)	4 (3%)	0
Terminated Study Participation through Week 24	9 (8%)	6 (4%)	3 (2%)
Withdraw Consent	5 (4%)	4 (3%)	1 (1%)
Lost to follow-up	1 (1%)	1 (1%)	0
Other	3 (3%)	1 (1%)	2 (1%)
After Week 16 (Early Escape)*	62	169	174
After Week 16 (Early Escape)†	61	171	173

* Placebo → golimumab 50 mg; golimumab 50 mg → golimumab 100 mg
† re-analysis using Applicant's data: Subject ID 80150 should be classified as discontinued study agent at Week 14 since he stopped taking the drug at Week 8.
Source: Clinical Study Report, Table 7, 8 and 9, pages 75, 77, and 79, respectively

The Applicant reported several protocol violations. A total of 31 randomized subjects (8%) did not meet selection criteria, 99 randomized subjects (24%) have deviations in study agent administration, and potentially 120 subjects have clinical supply issues (Table 5). The Applicant reported that between October 2006 and February 2007, they experienced significant issues associated with the availability of clinical supplies. The issues included difficulties in labeling, packaging, and distribution of sufficient quantities of study drug to meet the demands of these multiple studies. They reported that

> The impact of these issues was evaluated across all 5 studies and communicated to Health Authorities and investigative sites, including ECs/IRBs, on an ongoing basis during this period. As a result of the issues described above, disruptions in the study agent administration schedule occurred for some subjects in this study. To help affected study sites maintain the Protocol-specified dosing schedule during this period, the Applicant provided, wherever possible, a schedule to manage the study visits of each subject at a site based on the availability of study agent. The recommendation for rescheduling was based on the original subject visit schedule according to their date of randomization. To address the clinical supply availability issues, Centocor reviewed internal processes, including study agent forecasting, and conducted vendor audits to determine sources contributing to the availability problem. Corrective actions were taken to ensure availability of study agent.

In order to ensure that none of these violations affected the efficacy results, re-analyses excluding these subjects were performed.

Table 5: Number of subjects (%) with Protocol Deviations – Study C0524T08

		Golimumab	
	Placebo	50 mg	100 mg
Subjects Randomized	113	146	146
Subjects who did not meet selection criteria †	7 (6%)	15 (10%)	9 (6%)
Subjects with study agent administration deviation	25 (22%)	36 (25%)	38 (26%)
Received incorrect study agent or dose	0	0	1 (1%)
Missed an administration	9 (8%)	5 (3%)	8 (6%)
Received scheduled administration outside protocol-specified window	17 (15%)	32 (22%)	33 (23%)
Possible Clinical Supply Issues ‡	8 (7%)	5 (3%)	7 (5%)
Other Deviations	2 (2%)	4 (3%)	3 (2%)
Study Agent Unblinding	1 (1%)	2 (1%)	0

† Based on the Table 10 of Clinical Study Report and the Errata in Section 15 of Study Report (page 185)
‡ re-analysis using Applicant's data; possible clinical supply issues is a subset of missed an administration
Source: Clinical Study Report, Table 10 and 11, pages 82 and 84, respectively

Demographic characteristics of subjects at baseline were generally well balanced across treatment groups (Appendix 1). The majority of subjects were men (60%) and Caucasian (97%). The median age was 47 years and median weight was 84 kg. Clinical disease characteristics at baseline, including duration of PsA and psoriasis (Appendix 3), as well as baseline clinical characteristics of PsA from both the ACR core set of outcome measurements (Appendix 4) and non-ACR core set of outcome measurements (Appendix 5) were also generally similar across the randomized groups. Subjects were stratified to treatment by baseline MTX usage and approximately half of the subjects in each treatment group were receiving MTX at baseline. The following are some of the observations reported by the Applicant.

- The placebo group included a greater proportion of subjects with polyarticular arthritis with no rheumatoid nodules and a lower proportion of subjects with asymmetric peripheral arthritis than the combined golimumab group.
- The majority of subjects (70% in the placebo and 74% in the combined golimumab groups) had ≥ 3% BSA involvement with psoriasis; the median BSA in these subjects was 8% (range 3, 62) in the placebo group and 10% (range 3, 99) in the combined golimumab group.
- The median duration of psoriasis (about 17 years in the placebo and the combined golimumab groups) was substantially greater than the median duration of PsA (5 years in the placebo and the combined golimumab groups).

According to Dr. Brodsky, these observation are of no concern and do not affect the overall conclusion.

Both the SF-36 physical and mental component mean summary scores at baseline, as well as subject's comorbidities were similar across all treatment groups.

In terms of medications and/or therapies, the proportion of subjects who had taken prior medications for PsA, as well as the proportions of subjects at baseline using MTX, oral corticosteroids, or NSAIDs, specifically for PsA were generally similar across all treatment groups.

3.1.1.2.2 Primary Efficacy Endpoint

The proportion of subjects achieving an ACR 20 response at Week 14 in the combined golimumab group (48%) was greater than the proportion in the placebo group (9%), see Table 6. Pairwise comparisons between each golimumab dose groups and placebo demonstrated that the proportions of subjects achieving an ACR 20 response in each of the golimumab groups were also greater than the proportion in the placebo group. Of note, the proportion of subjects achieving an ACR 20 response is higher in the golimumab 50 mg group (51%) compared to golimumab 100 mg group (45%).
The proportions of subjects achieving an ACR 20 response in the golimumab groups were generally similar regardless of MTX use at baseline. However, a greater proportion of subjects in the placebo group receiving MTX achieved an ACR 20 response compared to those not receiving MTX.

Table 6: Number of subjects (%) who achieved an ACR 20 response at Week 14 stratified by baseline MTX use – Study C0524T08 (Applicant's)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
ACR 20				
n	113	146	146	292
Subjects in response	10 (8.8%)	74 (50.7%)	66 (45.2%)	140 (47.9%)
p-value		< 0.001	< 0.001	< 0.001
Subjects receiving MTX at baseline				
n	55	71	71	142
Subjects in response	8 (14.5%)	38 (53.5%)	32 (45.1%)	70 (49.3%)
Subjects not receiving MTX at baseline				
n	58	75	75	150
Subjects in response	2 (3.4%)	36 (48.0%)	34 (45.3%)	70 (46.7%)

Source: Clinical Study Report, Table 18 page 116

The Applicant conducted five sensitivity analyses including three planned and two post-hoc analyses.

The following are the planned analyses:

1. Subjects who discontinued due to AEs were considered nonresponders.
2. Subjects with insufficient data to determine ACR 20 response were considered nonresponders.
3. The analysis was based on observed data only

In the post hoc analyses,

4. Subjects who missed at least one administration of study agent for any reason prior to Week 14 were considered nonresponders
5. Subjects who missed at least one administration of study agent for any reason prior to Week 14 were excluded

The results are presented in Table 7. All five analyses supported the result of the primary endpoint analysis. The proportion of subjects achieving an ACR 20 response in the combined golimumab group and in each of the individual golimumab groups in each analysis remained greater than the proportion in the placebo group.

Table 7: Number of subjects (%) who achieved an ACR 20 response at Week 14 (Sensitivity Analyses) – Study C0524T08 (Applicant's)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	113	146	146	292
ACR 20 (Primary)	10 (9%)	74 (51%)	66 (45%)	140 (48%)
Sensitivity Analyses				
# 1 (AE as non-responder)	10 (9%)	72 (49%)	66 (45%)	138 (47%)
# 2 (Insufficient data as nonresponder)	9 (8%)	74 (51%)	66 (45%)	140 (48%)
# 3 (Observed data only)	9/106 (9%)	74/143 (52%)	66/144 (46%)	140/287 (49%)
# 4 (Missed at least one administration of study agent as nonresponders)	10 (9%)	74 (51%)	63 (43%)	137 (47%)
# 5 (Excludes subject with at least one missed administration of study agent)	10/105 (10%)	74/146 (51%)	63/142 (44%)	137/288 (48%)

Source: Clinical Study Report, Attachments 3.3 – 3.7, pages 390 – 395

A minor discrepancy was observed on the Applicant's efficacy datasets (Appendix 6). One placebo subject (ID 80530) should have been classified as 'ACR 20 nonresponder' instead of 'ACR 20 responder'. Although this did not affect the overall conclusion, the corrected result is reported and all the analyses that follow used this correct classification on subject 80530.

The proportions of subjects achieving an ACR 20 response in the golimumab groups were generally similar regardless of MTX use at baseline. However, a greater proportion of subjects in the placebo group receiving MTX versus not receiving MTX achieved an ACR 20 response.

Table 8: Number of subjects (%) who achieved an ACR 20 response at Week 14 (Re-Analyses) – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	113	146	146	292
ACR 20 (Primary)	9 (8%)	74 (51%) <0.0001	66 (45%) <0.0001	140 (48%) <0.0001
MTX* at Baseline	55	71	71	142
ACR 20	7 (13%)	38 (54%)	32 (45%)	70 (49%)
Non-MTX at Baseline	58	75	75	150
ACR 20	2 (3%)	36 (48%)	34 (45%)	70 (47%)

*Breslow-Day test of homogeneity across MTX strata was not significant (i.e. no interaction).

Additional analyses were conducted to assess the sensitivity of the primary analysis of ACR 20 response by assigning non-responder status to subjects who discontinued study agent, as well as by excluding subjects with different protocol violations. The results are reported in Table 9. All five analyses

supported the result of the primary endpoint analysis. The proportion of subjects achieving an ACR 20 response in the combined golimumab group and in each of the individual golimumab groups in each analysis remained greater than the proportion in the placebo group.

Table 9: Number of subjects (%) who achieved an ACR 20 response at Week 14 (Additional Analyses) – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	113	146	146	292
ACR 20 (Primary)	9 (8%)	74 (51%) <0.0001	66 (45%) <0.0001	140 (48%) <0.0001
Sensitivity Analyses				
# 1 (Discontinued study agent as non-responder)	9 (8%)	72 (49%) <0.0001	65 (45%) <0.0001	137 (47%) <0.0001
# 2 (Exclude subject who did not meet selection criteria)	9/106 (9%)	67/131 (51%)	59/137 (43%)	126/268 (47%)
# 3 (exclude subject with study agent administration deviation)	5/88 (6%)	52/110 (47%)	42/108 (39%)	94/218 (43%)
# 4 (exclude subject with possible clinical supply issues)	9/105 (9%)	71/141 (50%)	61/139 (44%)	132/280 (47%)
# 5 (subject with any protocol violations)	5/82 (6%)	47/98 (48%)	38/102 (37%)	85/200 (43%)

3.1.1.2.3 Secondary Endpoints

The Applicant conducted analyses of the secondary endpoints (see results below). Although all the results were in favor of golimumab dose groups, there are concerns with regards to some of these endpoints. Of note, a claim of 'skin psoriasis' using PASI75, is beyond the intent of this application which is to evaluate psoriatic arthritis patients and the risk-benefit profile for psoriasis in this population is unknown. Another concern is the lack of a strategy to control the Type 1 error when multiple secondary endpoints are being evaluated (e.g. SF36-PCS). Although the results are reported in this review, I have strong reservations about including these results in the label.

ACR 20 at Week 24

The proportion of subjects achieving an ACR 20 response at Week 24 in the combined golimumab group (57%) and in each of the individual golimumab groups was greater for all comparisons than the proportion in the placebo group (12%). The last observed value prior to early escape for subjects in the placebo group and golimumab 50 mg group who entered early escape was used to calculate ACR 20 response at Week 24.

In contrast to the ACR 20 response at Week 14, the proportion of subjects achieving an ACR 20 response at Week 24 is higher in the golimumab 100 mg group (61%) compared to golimumab 50 mg group (52%).

Table 10: Number of subjects (%) who achieved an ACR 20 response at Week 24 – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
ACR 20				
n	113	146	146	292
Subjects in response	14 (12.4%)	76 (52.1%)	89 (61.0%)	165 (56.5%)
p-value		< 0.001	< 0.001	< 0.001

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Source: Clinical Study Report, Table 19, page 118

Additional analyses were conducted to assess the sensitivity of the analysis of ACR 20 response at Week 24 that includes the following:

1. Subjects who entered early escape regardless of treatment group are considered 'nonresponders'.
2. The analysis is based on data reported at Week 24 regardless of subjects entering early escape.
3. Subjects who discontinued the study are considered 'nonresponder'. For subjects who entered early escape, the last observed value prior to early escape in the placebo group and golimumab 50 mg group was used to calculate ACR 20 response.

The results are presented in Table 11. All three analyses supported the result of the endpoint analysis at Week 24. The proportion of subjects achieving an ACR 20 response in the combined golimumab group and in each of the individual golimumab groups in each analysis remained greater than the proportion in the placebo group.

Table 11: Number of subjects (%) who achieved an ACR 20 response at Week 24 (Sensitivity Analyses) – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	113	146	146	292
ACR 20 at Week 24 (LOCF for early escape)	14 (12%)	76 (52%)	89 (61%)	165 (57%)
Sensitivity Analyses				
ACR 20 at Week 24 (from visit data)	14 (12%)	74 (51%)	89 (61%)	163 (56%)
# 1 (Early Escape as non-responder)	14 (12%)	76 (52%)	89 (61%)	165 (57%)
# 2 (Observed data at Week 24)	38/105 (36%)	78/138 (57%)	89/145 (61%)	167/283 (59%)
# 3 (Discontinue study agent as nonresponder)	14 (12%)	74 (51%)	85 (58%)	159 (54%)

PASI 75 Response at Week 14

A subset analysis of Psoriasis Area and Severity Index (PASI) was conducted on subjects with at least 3% body surface area (BSA) psoriasis skin involvement at baseline. According to the Applicant's cited reference, PASI is used to assess and grade the severity of psoriatic lesions and their response to therapy. PASI 75 is a dichotomous endpoint (whether or not a subject achieves at least 75% improvement from baseline in PASI score).

The proportion of subjects with ≥ 3% BSA psoriasis skin involvement at baseline who achieved a PASI 75 response at Week 14 was greater in the combined golimumab group (49%) and in each of the individual golimumab groups than in the placebo group (3%). A larger proportion of subjects achieved a PASI 75 response at Week 14 in the golimumab 100 mg group (58%) than in the 50 mg group (40%). Of note, PASI scores that were missing were considered 'non-PASI 75-responder', except on three subjects (two from placebo and one from golimumab 100 mg). Re-coding these subjects and re-analysis of the data showed no difference in the conclusion.

Table 12: Number of subjects with PASI 75 response at Week 14; randomized subjects with >= 3% BSA psoriasis skin involvement at baseline – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Randomized subjects with ≥ 3% BSA psoriasis skin involvement at baseline	79	109	108	217
PASI 75				
n	79	109	108	217
Subjects in response	2 (2.5%)	44 (40.4%)	63 (58.3%)	107 (49.3%)
p-value		< 0.001	< 0.001	< 0.001

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Source: Clinical Study Report, Table 20, page 120

Improvement from Baseline in the HAQ Score at Week 24

The improvement from baseline in the HAQ score at Week 24 was greater in the combined golimumab group and in each of the individual golimumab groups than in the placebo group (Table 13). The proportions of HAQ responders achieving a ≥ 0.22 or a ≥ 0.3 improvement from baseline at Week 24 were also greater in the combined golimumab group and in each of the individual golimumab groups than in the placebo group. Of note, in the Applicant's analysis, they applied the last observed value prior to escape to subjects who entered early escape and applied the last observed value to subjects who discontinued study treatment.

Sensitivity analyses were conducted to assess the effect of subjects discontinuing study treatment before the end of the study. One analysis is conducted using only available HAQ scores at Week 24 and the second analysis is conducted applying the baseline HAQ score to subjects who discontinued study treatment (prior to Week 24) to the Week 24 HAQ score. These results (presented in Table 13) are consistent with the Applicant's results.

Table 13: Summary of improvement from baseline in HAQ score at Week 24; randomized subjects – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	113	146	146	292
Applicant's Result (LOCF)*				
N	113	146	146	292
Mean ± SD	-0.01 ±0.5	0.3 ±0.6	0.4±0.5	0.4 ±0.5
n(%) with Δ change from baseline at Week 24 ≥ 0.3	26 (23%)	63 (43%)	76 (52%)	139 (48%)
p-value		0.0007	<0.0001	<0.0001
n(%) with Δ change from baseline at Week 24 ≥ 0.22	33 (29%)	74 (51%)	90 (62%)	164 (56%)
p-value		0.0005	<0.0001	<0.0001
Sensitivity Analyses				
# 1: BOCF				
N	113	146	146	292
Mean ± SD	-0.00 ±0.4	0.3 ±0.6	0.4±0.5	0.4 ±0.5
n(%) with Δ change from baseline at Week 24 ≥ 0.3	24 (21%)	60(41%)	75 (51%)	135 (46%)
p-value		0.0007	<0.0001	<0.0001
n(%) with Δ change from baseline at Week 24 ≥ 0.22	31 (27%)	69 (47%)	88 (60%)	157 (54%)
p-value		0.0012	<0.0001	<0.0001
# 2 (Observed data at Week 24)				
N	104	139	143	282
Mean ± SD	-0.03 ±0.5	0.3 ±0.6	0.4±0.5	0.4 ±0.5
n(%) with Δ change from baseline at Week 24 ≥ 0.3	23 (22%)	60 (43%)	74 (52%)	134 (48%)
p-value		0.0006	<0.0001	<0.0001
n(%) with Δ change from baseline at Week 24 ≥ 0.22	30 (29%)	69 (50%)	88 (62%)	157 (56%)
p-value		0.0011	<0.0001	<0.0001

Source: Clinical Study Report, Table 21, page 121
p-value is unadjusted

Physical Component Summary Score of the SF-36 at Week 14

The change from baseline in SF-36 PCS scores at Week 14 was greater in the combined golimumab group and in each of the individual golimumab groups than in the placebo group. A numerically greater mean change was observed in the golimumab 100 mg group than in the 50 mg group. Three subjects (two in golimumab 50 mg and one in golimumab 100 mg) had slightly different result when the data was re-analyzed; however, this did not affect the overall conclusion. Of note, baseline PCS score was applied to subjects who discontinued from the study prior to Week 14.

Table 14: Summary of change from baseline in SF-36 physical component summary scores at Week 14; randomized subjects

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Change from baseline				
n	113	146	146	292
Mean ± SD	0.63 ± 7.676	6.53 ± 8.882	7.85 ± 9.547	7.19 ± 9.229
Median	0.00	5.45	6.80	5.95
IQ range	(-3.50, 5.40)	(0.30, 12.90)	(0.50, 14.70)	(0.50, 14.15)
Range	(-22.8, 22.4)	(-26.6, 27.1)	(-9.5, 32.7)	(-26.6, 32.7)
p-value		< 0.001	< 0.001	< 0.001

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Source: Clinical Study Report, Table 22, page 122

3.1.1.2.4 Additional Analyses to Support the Primary Efficacy Analysis

ACR 50 and ACR 70 at Week 14 and Week 24

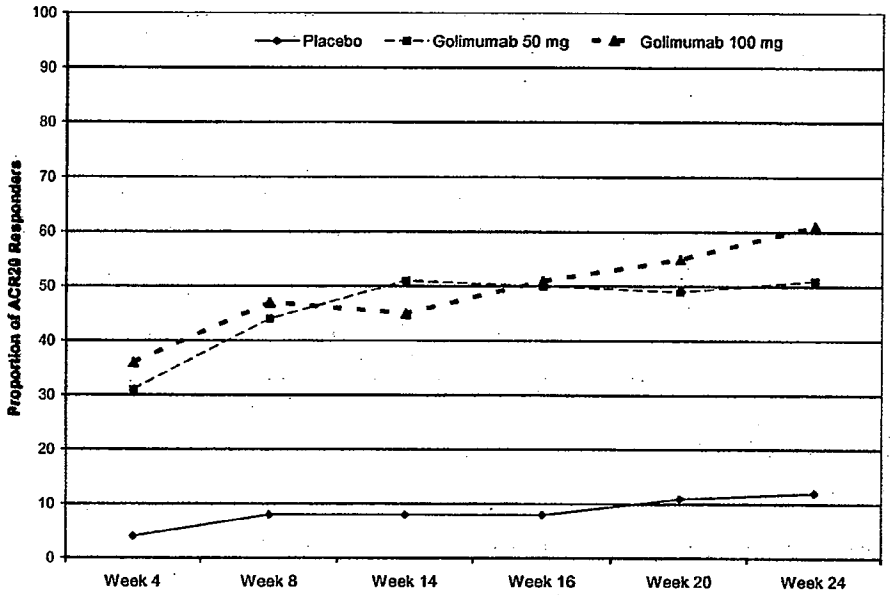
The proportion of subjects achieving either an ACR 50 or ACR 70 response at Week 14 or at Week 24 is shown in Appendix 7 and in Figure 3 and Figure 4. There was a greater proportion of ACR 50 and ACR 70 responder in each of the individual golimumab groups than in the placebo group.

ACR 20, ACR 50, and ACR 70 over time

The proportions of subjects with an ACR 20 response, ACR 50 response, and ACR 70 response at weeks 4, 8, 14, 16, 20 and 24 are presented in Figure 2 to Figure 4. A summary of ACR 20 response rates over time can be found in Appendix 7. In Appendix 7, I presented both the Applicant's results which includes data after subject discontinued study agent, and the results from re-analyses which assumes that subject who discontinued study agent are nonresponders. Both the Applicant's analyses and my re-analyses applied the early escape rule. Note that there is slight discrepancy between the Applicant's result (using all available data) and my results (discontinue study agent as non-responder) and both are presented in Appendix 7; however, the results and the overall conclusion are generally similar.

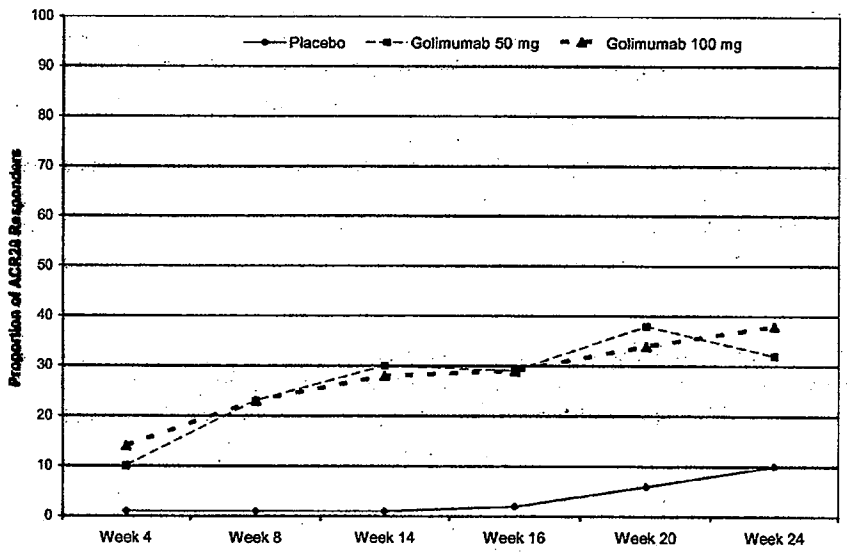
By Week 4, a greater proportion of ACR 20 responders in each of the individual golimumab groups than in the placebo group were observed. There is no noticeable difference in the proportion of responders between golimumab 50 mg and golimumab 100 mg except at Week 14 (which slightly favors golimumab 50 mg) and after Week 20 (which favors golimumab 100 mg).

Figure 2: Proportion of ACR 20 responders over time



Like ACR 20 responders, by Week 4, there was a greater proportion of ACR 50 responder in each of the individual golimumab groups than in the placebo group. There is no noticeable difference in the proportion of responders between golimumab 50 mg and golimumab 100 mg over time.

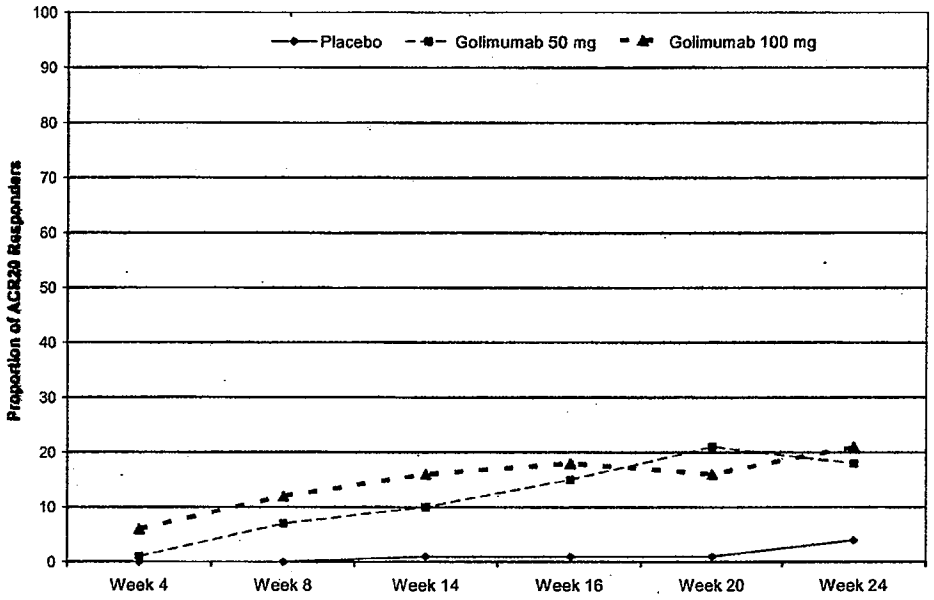
Figure 3: Proportion of ACR 50 responders over time



When a more stringent criteria is used (i.e. ACR 70), there was a greater proportion of ACR 70 responder in golimumab 50 mg group than in the golimumab 100 mg group or placebo group prior to

early escape. After Week 16, there is no big difference in the proportion of responders between golimumab 50 mg and golimumab 100 mg, and both groups have greater proportion of ACR 70 responder than in the placebo group.

Figure 4: Proportion of ACR 70 responders over time



ACRn Index of Improvement

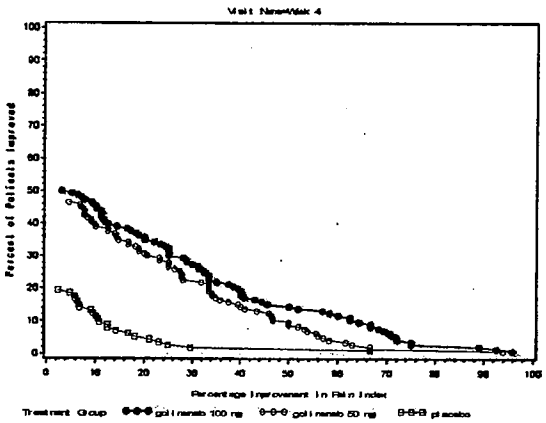
Continuous responder curves for each treatment arm were plotted for the ACRn scores at weeks 4, 8, 14, 16, 20, and 24 (Figure 5. ACRn is a specific percentage response achieved by a subject using the ACR response criteria. The derivation rule is described in Appendix 6.

Note that in these plots, all subjects who drop out of the study are considered non-responders after the time of dropout. There are instances where subjects discontinue from taking the study drug but remain in the trial and are continuously assessed for disease activity response (i.e. retrieved drop-out). These efficacy measures are included in the calculation of ACRn. Meanwhile, in subjects who entered early escape, last observed value prior to escape was used to calculate ACRn. These figures were created to provide a visual display of the relative benefit of various doses across the entire range of responses. The x-axis shows the percent ACR response achieved at week 24 (i.e. percentage improvement in disease activity), and the y-axis shows the corresponding percentage of subjects achieving that level of response.

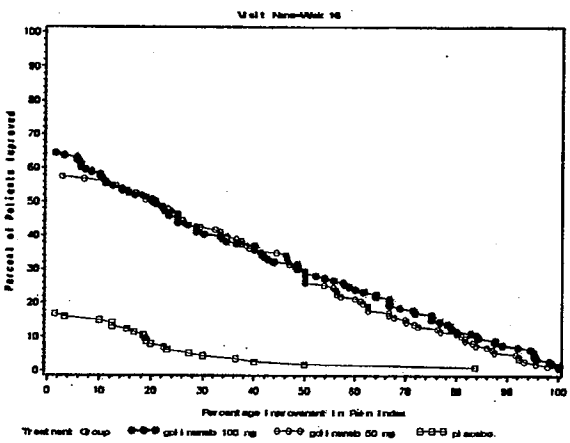
In all studies, there is a clear separation of curves between the golimumab groups and placebo over time and using different criteria of response. After Week 8, there is higher proportion of subjects in the golimumab groups responding than in the placebo group, even when the most stringent criteria is used (i.e. >70 response). There is no clear separation of curves between golimumab 50 mg and golumimab 100 mg which suggests that golimumab 50 mg is effective in reducing signs and symptoms of PsA.

Figure 5: Response Profile by Week – Study C0524T08
Green: Placebo, Red: Golimumab 50 mg, and Black: Golimumab 100 mg

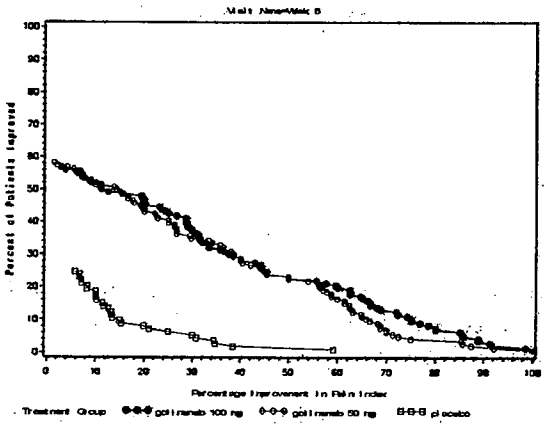
Week 4



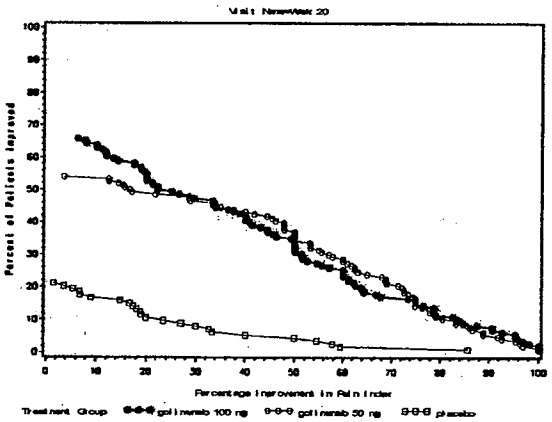
Week 16



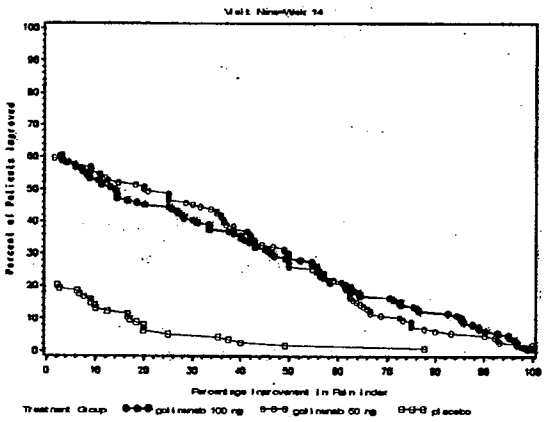
Week 8



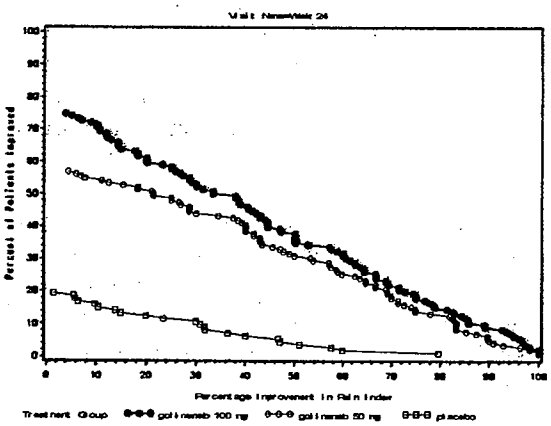
Week 20



Week 14



Week 24



Maintenance of Effect

An alternate way to view the treatment effect over time is to explore those subjects who responded to treatment at Week 24, using the ACR 20 responder criteria. In the following two graphs (Figure 6 and Figure 7), we examined when these subjects started to respond to treatment and how often they respond to the treatment. In some cases, subjects may respond early and then respond late again while some respond all throughout the study. In Figure 6, we assume that a subject who responded will respond up to the end of the study. Therefore the x-axis shows the week the subject started to respond, and the y-axis shows the proportion of subjects who are classified as ACR 20 responder at that timepoint. In Figure 7, since there are a total of 6 study visits, the x-axis corresponds to the frequency of visits the subject had an ACR 20 response and the y-axis shows the proportion of subjects who are classified as ACR 20 responder. In general, each subject has a minimum of one visit that the subject is classified as ACR 20 responder (at Week 24). A subject could be responding in all visits, therefore will be in the '>5' category; or a subject could be responding in 5 out of 6 visits and will be in the '<4' category.

A total of 179 subjects were classified as ACR 20 responder at Week 24. Among these responders, there is evidence that most subjects receiving golimumab 50 mg or golimumab 100 mg achieved the level of response (i.e. ACR 20) as early as Week 4 (Figure 6). It some cases, subjects receiving golimumab 100 mg continue to benefit even at Week 24. In terms of maintenance, more than 60% of subjects in golimumab 100 mg and more than 80% of subjects in golimumab 50 mg who responded at Week 24 were responders at least 4 out of the 6 visits (Figure 7).

Figure 6: Start Time of ACR 20 Responders– Study C0524T08

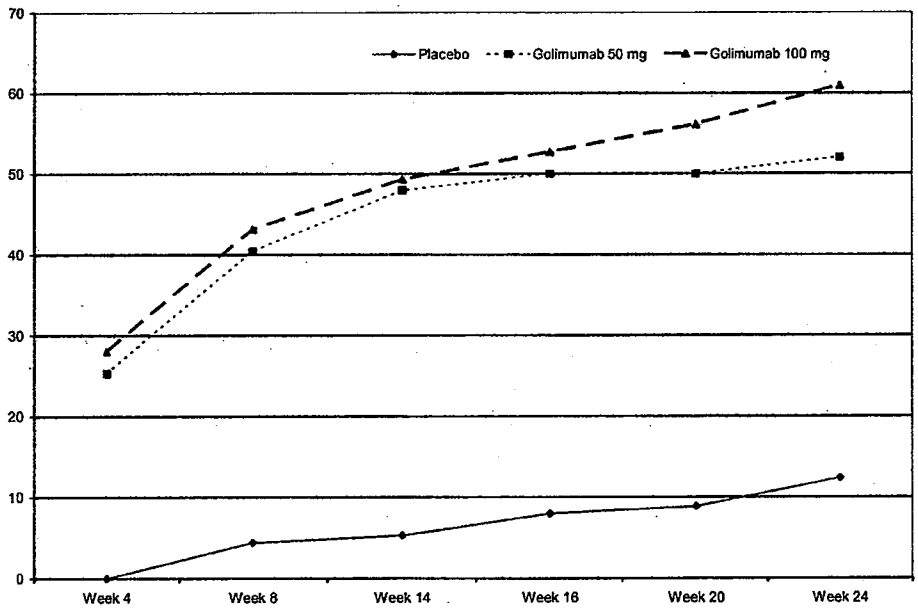
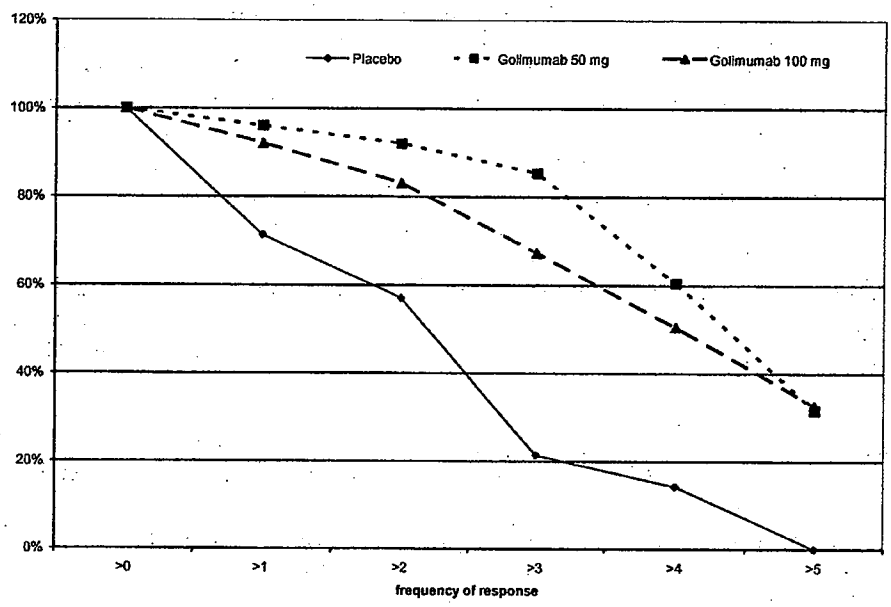


Figure 7: Frequency of Responses among Subjects Classified as ACR 20 Responders– Study C0524T08



ACR Component

The seven components of the ACR response are: swollen and tender joint count, subject's assessment of pain (by VAS), subject's and physician's global assessment of disease activity (by VAS), HAQ, and CRP. The percent improvement from baseline for each of the components at Week 14 and at Week 24 is reported in Appendix 8 and Appendix 9, respectively. The median percent improvement from baseline for every component was greater in the combined golimumab group and in each of the individual golimumab groups than in the placebo group at Week 14. This difference was also seen at Week 24.

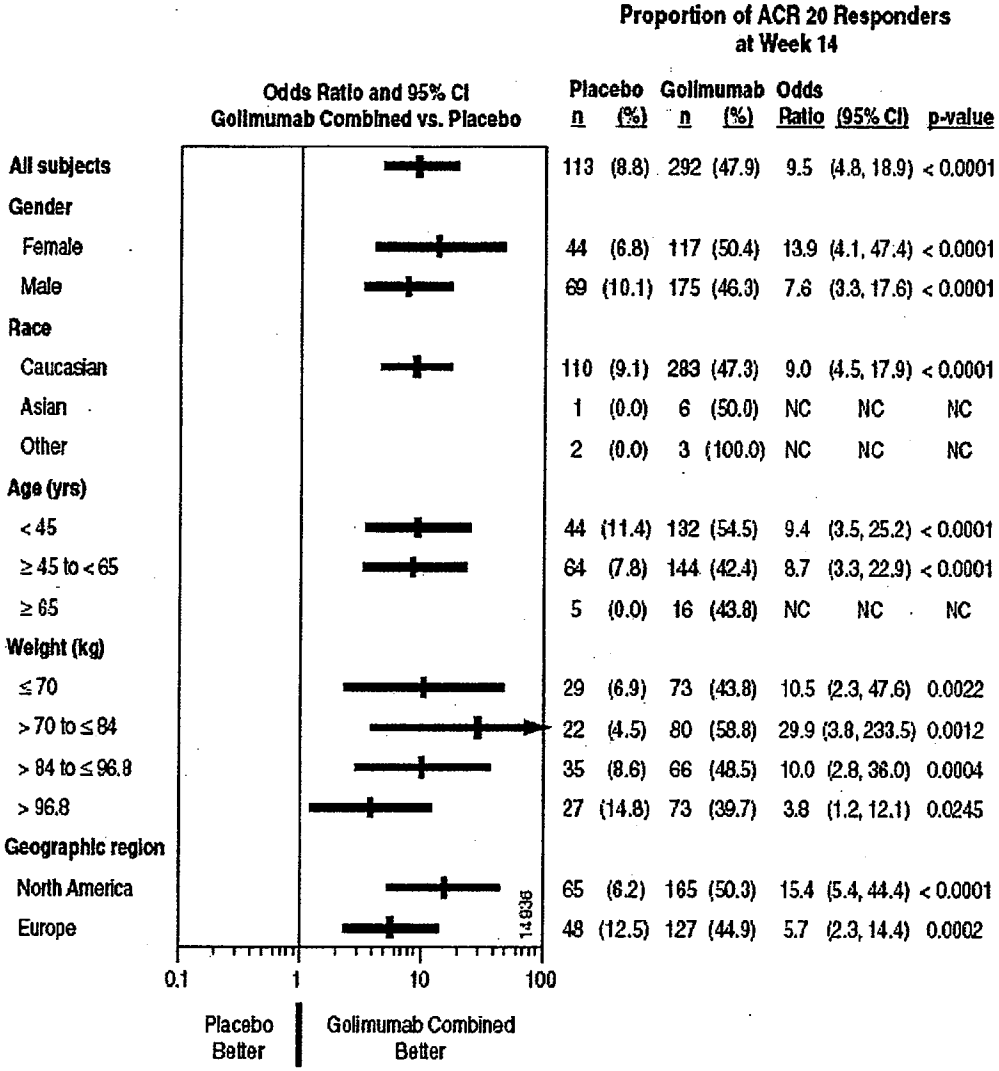
3.1.1.2.5 Findings in Subgroups and Special Population

The Applicant conducted subgroup analyses on the primary endpoint (i.e. ACR 20 at Week 14). In the report, the Applicant calculated the odds ratios and corresponding CIs in subgroups for demographic and baseline disease characteristics and the use of certain medications. They used the following criteria to interpret the results:

> An odds ratio greater than 1 corresponds to an observed ACR 20 response rate that was greater with golimumab than with placebo. Subgroup odds ratios with CIs that overlap the CI for all subjects indicate treatment effect within the subgroup was consistent with the treatment effect observed in the overall study population.

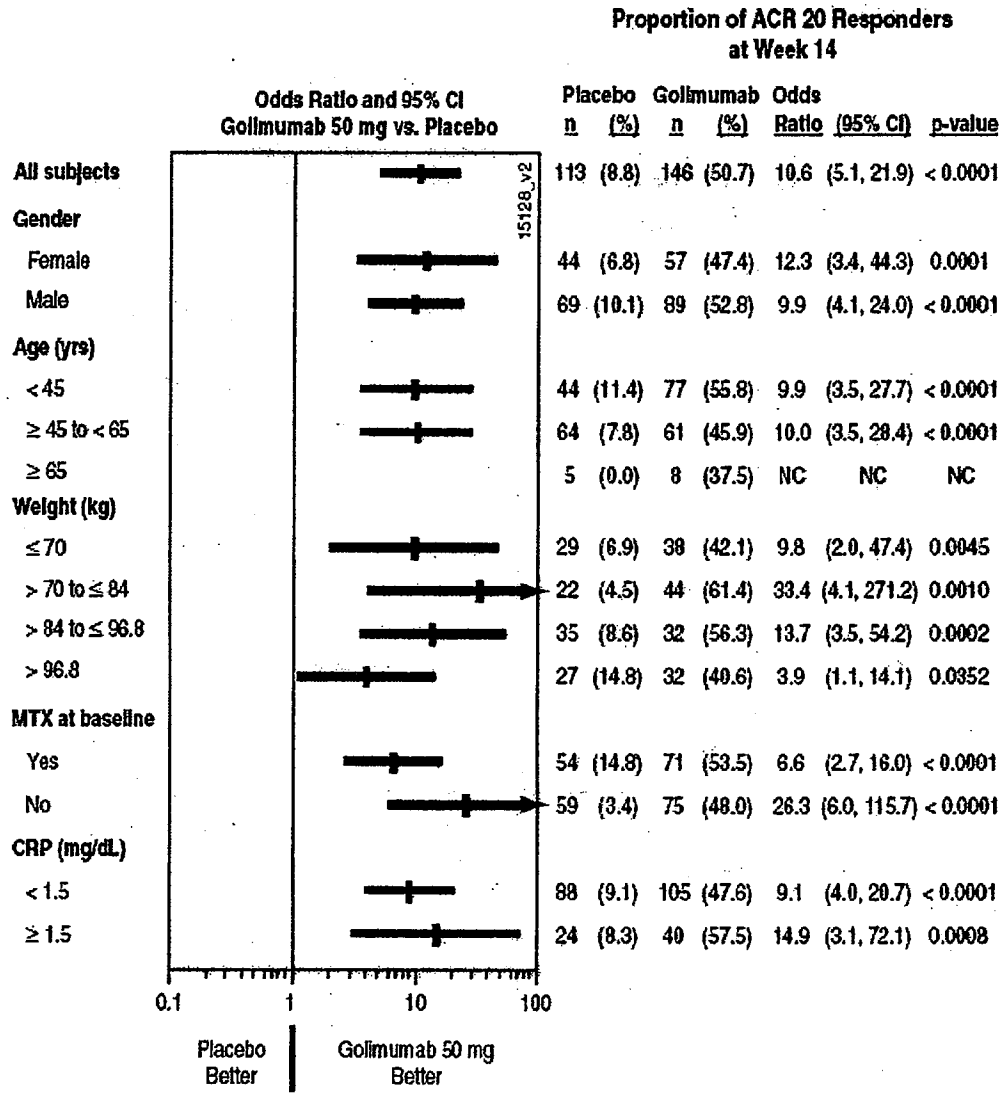
The following figures (Figure 8 to Figure 10) are the odds ratios and 95% CIs for ACR 20 response by subgroup based on demographic characteristics. Treatment benefits with golimumab (combined or individually) versus placebo appear to be consistent in all subgroups.

Figure 8: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the golimumab **combined** group versus the placebo group for subgroups defined by demographic characteristics; randomized subjects



Source: Clinical Study Report, Attachment 3.70 page 481

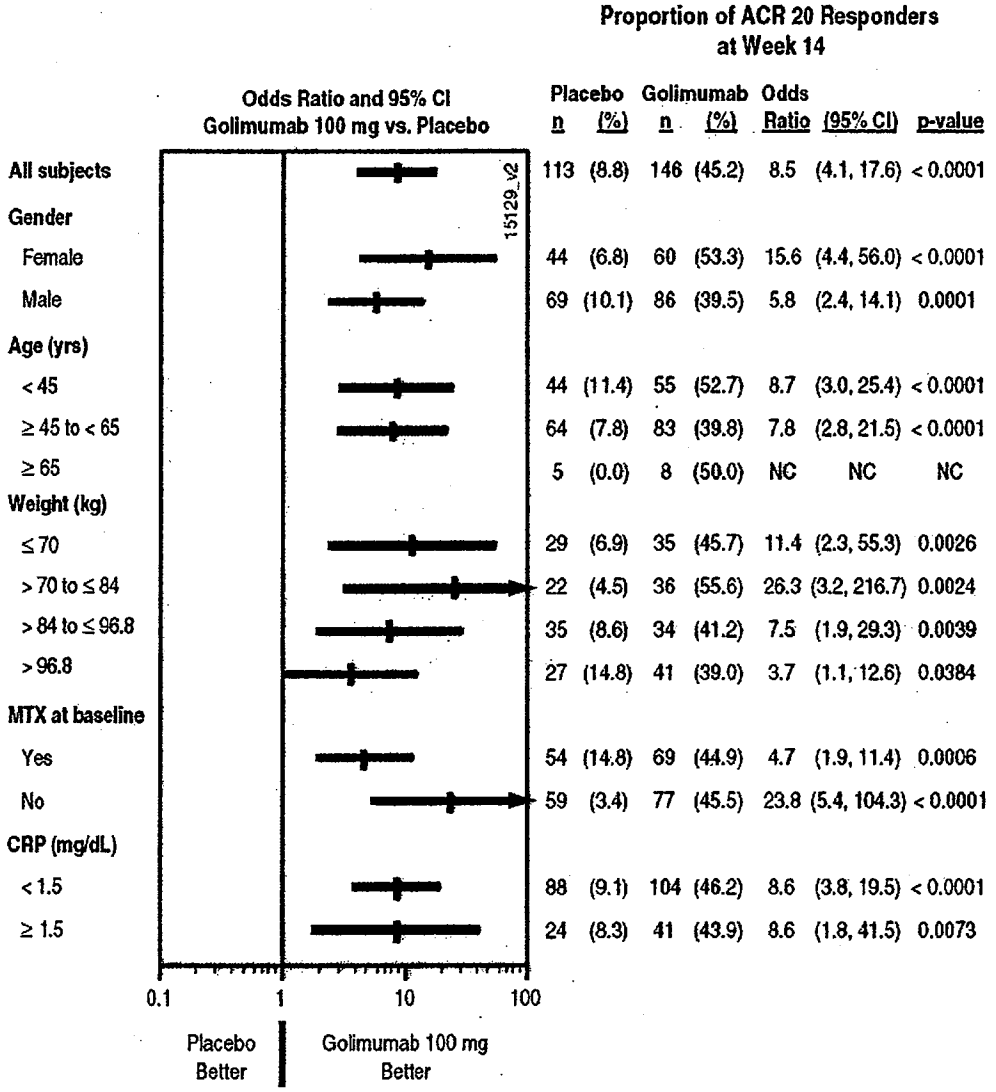
Figure 9: Odds ratio (vertical bars) and 95 % confidence intervals (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the **golimumab 50 mg group** versus the placebo group for selected subgroups; randomized subjects



	Placebo n	Placebo (%)	Golimumab n	Golimumab (%)	Odds Ratio	(95% CI)	p-value
All subjects	113	(8.8)	146	(50.7)	10.6	(5.1, 21.9)	< 0.0001
Gender							
Female	44	(6.8)	57	(47.4)	12.3	(3.4, 44.3)	0.0001
Male	69	(10.1)	89	(52.8)	9.9	(4.1, 24.0)	< 0.0001
Age (yrs)							
< 45	44	(11.4)	77	(55.8)	9.9	(3.5, 27.7)	< 0.0001
≥ 45 to < 65	64	(7.8)	61	(45.9)	10.0	(3.5, 28.4)	< 0.0001
≥ 65	5	(0.0)	8	(37.5)	NC	NC	NC
Weight (kg)							
≤ 70	29	(6.9)	38	(42.1)	9.8	(2.0, 47.4)	0.0045
> 70 to ≤ 84	22	(4.5)	44	(61.4)	33.4	(4.1, 271.2)	0.0010
> 84 to ≤ 96.8	35	(8.6)	32	(56.3)	13.7	(3.5, 54.2)	0.0002
> 96.8	27	(14.8)	32	(40.6)	3.9	(1.1, 14.1)	0.0352
MTX at baseline							
Yes	54	(14.8)	71	(53.5)	6.6	(2.7, 16.0)	< 0.0001
No	59	(3.4)	75	(48.0)	26.3	(6.0, 115.7)	< 0.0001
CRP (mg/dL)							
< 1.5	88	(9.1)	105	(47.6)	9.1	(4.0, 20.7)	< 0.0001
≥ 1.5	24	(8.3)	40	(57.5)	14.9	(3.1, 72.1)	0.0008

Source: Clinical Study Report, Attachment 3.74 page 484

Figure 10: Odds ratio (vertical bars) and 95 % confidence intervals (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the **golimumab 100 mg group** versus the placebo group for selected subgroups; randomized subjects



Source: Clinical Study Report, Attachment 3.75 page 485

In Appendix 10 to Appendix 12, subgroups based on baseline disease and clinical characteristics, baseline PsA subtypes and baseline medication and prior therapies for PsA are presented. Like the demographic characteristics, treatment benefit with golimumab versus placebo appear to be consistent in all subgroups, with the exception of the subgroup with a PsA duration of <1 year, which had only a small number of subjects available for evaluation.

3.1.1.2.6 Efficacy Conclusion

In Study C0524T08, there is evidence that golimumab 50 mg and golimumab 100 mg administered SC every four (q4) weeks in subjects with active PsA and who had not previously been treated with anti-TNF therapy reduces signs and symptoms of PsA. This is based on the result from the analysis of the primary endpoint (i.e. ACR 20 at Week 14). In addition, the proportions of subjects achieving an ACR 20 response in the golimumab groups were generally similar regardless of MTX use at baseline. However, a greater proportion of subjects in the placebo group receiving MTX versus not receiving MTX achieved an ACR 20 response. The evidence is also supported by the results from the analyses of other endpoints (e.g. ACR 50, ACR70, ACRn index of improvement, and all ACR components), as well as result from the analysis of the ACR 20 at Week 24.

Although no formal analysis was conducted to compare golimumab 50 mg and golimumab 100 mg, numerically there is generally no difference in the proportion of ACR 20 responders between the two golimumab dose groups at Week 14. There is no additional treatment benefit with the 100 mg dose compared to the golimumab 50 mg dose based on submitted data at this time. This evidence is also supported by the results from the analyses of other endpoints (e.g. ACR 50, ACR70, ACRn index of improvement) at Week 14. In contrast, there is some evidence that at Week 24, there is higher proportion of ACR 20 responder in the golimumab 100 mg group compared to golimumab 50 mg. I refer the reader to Dr. Brodsky review for the benefit-risk profile of these doses. My recommendation is that patient should be administered golimumab 50 mg QD every four weeks.

When evaluating responder status throughout the 24-week treatment period (assessment starts at Week 4), there is evidence that most subjects receiving golimumab 50 mg or golimumab 100 mgachieved the level of response (i.e. ACR 20) as early as Week 4. In the 24-week treatment period comprised of 6 visits, more than 60% of subjects in golimumab 100 mg and more than 80% of subjects in golimumab 50 mg who responded at Week 24 were responders at least 4 out of the 6 visits. Thirty percent of subjects who responded at Week 24 maintained their response in all six visits (starting at Week 4). Therefore, there is evidence that subjects taking golimumab 50 mg maintained their responder status throughout the treatment period.

Secondary endpoints were also analyzed. These include PASI 75 to assess and grade the severity of psoriatic lesions and their response to therapy, and SF36-PCS to measure disease burden. Although the results from the analyses of these endpoints are in favor of golimumab over placebo, I have strong reservations about including these results in the label for the following reasons:

1. Skin psoriasis, as measured by PASI 75 is beyond the intent of this application that is to evaluate psoriatic arthritis patients. In addition, the risk-benefit profile for psoriasis in this population is unknown.
2. Another concern is on how to control the Type 1 error when multiple secondary endpoints are being evaluated (e.g. SF36-PCS).

3.1.2 ANKOLYSING SPONDYLITIS

3.1.2.1 Study Design and Analysis Plan

C0524T09 is the only Phase 3 study conducted by the Applicant to evaluate the efficacy and safety of golimumab in subjects with active Ankylosing Spondylitis (AS). The efficacy is evaluated by assessing reduction in signs and symptoms of active AS at Week 14. Subjects eligible for this study were men and

women with a diagnosis of AS based on the 1984 modified New York criteria with symptoms of moderate to severe disease activity for at least 3 months prior to first study agent administration. The study population had active AS despite current or previous DMARD or NSAID therapy and had not been treated previously with anti-TNFα therapy.

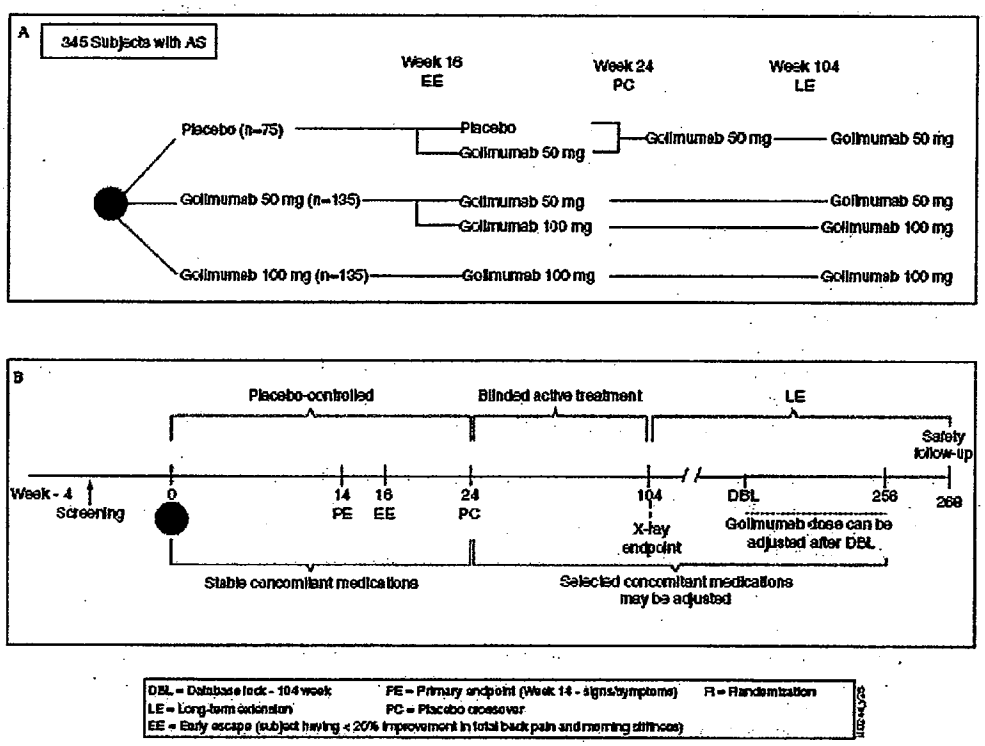
Study C0524T09 is currently ongoing and in this submission, the Applicant reported up to 24 weeks of data (placebo-controlled portion). Of note, all subjects were treated for at least 24 weeks or until they discontinued study agent or participation in the study.

The following is a brief summary of the study design.

> C0524T09 has 3 distinct periods (Figure 11):
>
> - Placebo-controlled period (Weeks 0 through 24), including Early Escape at Week 16
> - Blinded active treatment period (Weeks 24 through 52), beginning with the crossover of placebo subjects to golimumab 50 mg at Week 24 every four weeks
> - Starting with the Week 104 injection, subjects are to receive active treatment in a long-term extension of the study which ends at the Week 268 visit.
>
> The study was to be conducted at approximately 60 global investigational sites. Approximately 345 subjects were to be randomly assigned in a 1:1.8:1.8 ratio to 1 of 3 treatment groups: placebo, golimumab 50 mg or golimumab 100 mg. Treatment allocation will be by randomization via a centralized, interactive voice response system (IVRS) provided by [redacted] b(4)
>
> In order to ensure relatively even treatment balance within sites, within screening CRP level (≤1.5 mg/dL; >1.5 mg/dL) and within the study overall, subject allocation to a treatment group was performed using an adaptive stratified randomization design. The randomization method is minimization with biased-coin assignment. The measure used to calculate lack of balance in the minimization algorithm is the Variance. Weights for the balancing factors are Site (1), Screening CRP level (1), Overall Study (1). The probability of assignment to each treatment group based on the group with the lowest total imbalance measure is shown in Table 2. Note that the algorithm seeks to maintain balance only at the individual factor margins and not at the cross-classification cell levels. Thus, treatment balance within every stratum formed by the cross-classification of the balancing factors is not expected. A carton number will be assigned based on subject's treatment assignment.
>
> At Week 16, subjects in any group who had <20% improvement from baseline in both total back ppain and morning stiffness measures qualified to enter early escape in a double-blinded fashion. Treatment for subjects who entered early escape was as follows:
>
> Placebo → golimumab 50 mg SC injections at Weeks 16 and 20
> Golimumab 50 mg → golimumab 100 mg SC injections at Weeks 16 and 20
> Golimumab 100 mg → No change (golimumab 100 mg SC injections at Weeks 16 and 20)
>
> The IVRS will be used to qualify subjects for early escape. For the subjects who meet the early escape criteria, the carton number allocation will be based on their randomized treatment assignment and the corresponding changes associated with the treatment type due to early escape. For the subjects who do not meet the early escape criteria, the carton number allocation will continue to be of the treatment type based on their randomized treatment group.

The randomization strategy applied to this study is similar to the strategy used in the PsA study. Refer to Section Study Design and Analysis Plan3.1.1.1 for a more detailed description of this approach, the concerns and the Applicant's response to the request.

Figure 11: Study Design – C0524T09



Note: Panel A shows study treatments; Panel B shows key timepoints during the study.

Source: Clinical Study Report, page 27

The primary efficacy endpoint is the proportion of subjects achieving an Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. According to the Applicant,

> The ASsessment in Ankylosing Spondylitis (ASAS) International Working Group has developed the ASAS 20 response as an established validated criterion of short-term response. Furthermore, ASAS and the Spondylitis Association of America have published recommendations for using ASAS 20, ASAS 40 and ASAS 5/6 response criteria in AS clinical trials
>
> An ASAS 20 response was defined as
>
> 1. An improvement of ≥ 20% from baseline and absolute improvement from baseline of at least one on a 0 to 10 cm scale in at least 3 of the following 4 domains:
>   a. Subject Global
>   b. Total backpain
>   c. Function as measured by BASFI (Bath Ankylosing Spondylitis Functional Index)
>   d. Inflammation (average of the last 2 questions of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)concerning morning stiffness)
>
> 2. Absence of deterioration from baseline (deterioration defined as ≥ 20% worsening and absolute worsening of at least 1 on a 0 to 10 cm scale) in the potential remaining domain.
>
> In this primary efficacy analysis, data from all randomized subjects will be analyzed according to their assigned group.

Reduction in signs and symptoms of arthritis was evaluated by comparing the proportion of subjects with ASAS 20 response at Week 14 between the combined golimumab group (golimumab 50 mg and 100 mg groups combined) and the placebo group. A Cochran-Mantel-Haenszel (CMH) test with stratification by subjects' screening CRP ($\leq$1.5 mg/dL, >1.5 mg/dL) was performed for this analysis at a significance level of $\alpha = 0.05$. If this test was significant, pairwise comparisons between the golimumab 50 mg and placebo groups and between the golimumab 100 mg and placebo groups were performed using the same statistical procedure at a significance level of $\alpha = 0.05$ each.

The following is a summary of the data handling rules:

Treatment Failure Rules

Treatment failure rules were applied in the primary analysis. Subjects were considered to have not achieved an ASAS 20 response at Week 14 if, prior to Week 14, they:

- Initiated new DMARDs, biologics, systemic immunosuppressives for AS
- Increased the dose of SSZ, MTX or hydroxychloroquine above baseline level for AS.
- Initiated treatment with oral, IV, or IM corticosteroids for AS, or increased the dose of oral corticosteroids for AS above baseline dose.
- Discontinued study agent injections due to unsatisfactory therapeutic effect.

Missing Data Rules

Subjects with missing data for all of the ACR components at Week 14, were considered as ASAS 20 nonresponders at Week 14. If subjects had data for at least 1 ASAS component at Week 14, the following rules were applied:

- If an ASAS 20 component was missing from baseline through Week 14 then 0% was assigned as the percent improvement from baseline of that component.
- Any missing ACR component value at Week 14 was replaced by the last nonmissing observation (including baseline).
- Any missing baseline ACR component value (needed for computing percent improvement from baseline) was imputed as the median value of that component from all subjects with baseline data in the same stratum (screening CRP level).

Where the baseline value of a component was 0, for purposes of calculating ASAS 20, the change from baseline was determined as follows:

- If the postbaseline component value was also 0, then the percent change was set equal to 0.
- If the postbaseline component value was >0, then the percent change was calculated as though the baseline was 0.1.

For subjects who met early escape criteria at Week 16 in the placebo and golimumab 50 mg groups, the Week 24 ASAS 20 components, ASAS 40, ASAS 5/6, BASDAI, BASMI (Bath Ankylosing Spondylitis Metrology Index), and BASFI were overwritten with Week 16 values (last observed value prior to early escape). No change was made for subjects in the golimumab 100 mg group since these subjects had no change in dose.

Three sensitivity analyses were performed by the Applicant and they are the following:

- The first sensitivity analysis was performed as a more conservative assessment of efficacy. This sensitivity analysis was performed using the treatment failure and missing data imputation rules. In addition, subjects who discontinued study treatment because of an AE prior to Week 14 (subjects expected to be more likely to have been receiving golimumab) were also considered to have not achieved an ASAS 20 response at Week 14.

- The second sensitivity analysis was performed using the treatment failure, and zero-divisor rules were applied, with no imputation for missing data. Subjects with missing ASAS 20 components were considered to have not achieved an ASAS 20 response.

The third sensitivity analysis was performed using the observed data only. The zero-divisor rule was applied but the treatment failure and the missing data rules were not used. When values for some components were missing, the following conditions were considered to be failure to achieve an ASAS 20 response:

- If at least 2 of the observed components of ASAS showed <20% improvement;
- If at least 2 of the observed components of ASAS showed absolute improvement of less than 1;
- If 1 of the observed components showed less than 20% improvement, and a different observed component showed absolute improvement of less than 1;
- If any of the observed components of ASAS showed deterioration from baseline (≥ 20% worsening and absolute worsening of at least 1 on a 0 to 10 cm scale).

Subjects whose ASAS 20 response could not be determined were excluded from the analysis.

The 'major' secondary efficacy endpoints the Applicant evaluated are:

1. The proportion of subjects achieving an ASAS 20 at Week 24 was compared between groups. Subjects who met any of the treatment failure criteria prior to Week 24 were considered to have not achieved ASAS 20 response.
2. The change from baseline in BASFI at Week 14 was compared between groups.
3. The change from baseline in BASMI at Week 14 was compared between groups.

In the analysis of secondary efficacy endpoints,

Pearson's chi-square test was used to compare binary categorical data, and the Cochran-Mantel-Haenszel (CMH) chi-square test to compare binary categorical data with stratification (stratified by screening CRP level [≤1.5 mg/dL, >1.5 mg/dL]). Analysis of variance (ANOVA) on van der Waerden normal scores with treatment and subject's screening CRP level as factors in the model was used to compare continuous data, unless otherwise specified.

The first test compared golimumab at any dose (golimumab 50 mg and 100 mg combined) versus placebo. If the results were significant, then pairwise comparisons of golimumab 50 mg versus placebo and golimumab 100 mg versus placebo were made. This method protected the significance level at 0.05: a golimumab dose group that was nominally significantly better than the placebo group would not be reported as significant unless the combined golimumab groups were significantly better than the placebo group as well. All statistical testing was 2-tailed, at a significance level of 0.05. In addition to statistical analyses and tabulated descriptive statistics, graphical data displays (eg, box plots) and subject listings were also used to summarize/present the data.

3.1.2.2 Results and Discussion

3.1.2.2.1 Study Population and Demographic/Baseline Characteristics

A total of 356 subjects from 46 sites were randomly assigned to treatment (Table 15). It was reported that two subjects were randomized in the IVRS before the appropriate prerandomization procedures were completed; as a result they were reassigned as screen failures in the IVRS. One of these subjects was subsequently rescreened and rerandomized. One subject randomized to golimumab 50 mg (ID 90031) was never treated.

Of the 356 subjects, 186 (52%) were in North America, 83 (23%) in Asia and 87 (24%) in Europe. A total of 11 subjects discontinued study agent prior to Week 14, and only six additional subjects discontinued between Week 14 to Week 24, for a total of 17 subjects. A numerically greater proportion of subjects taking golimumab discontinued study agent through week 14 (and through week 24)

compared to subjects taking placebo. Of the 17 subjects who discontinued study agent, 10 subjects terminated study participation. See Appendix 1 for definition of 'discontinued study agent'.

At Week 16 (early escape), 41 (53%) subjects in the placebo group began receiving golimumab 50 mg and 25 (18%) subjects randomized to golimumab 50 mg began receiving golimumab 100 mg.

Of the 66 subjects who entered early escape at Week 16, only one subject in the golimumab 100 mg group discontinued study treatment through Week 24.

Table 15: Summary of Study Participating Status – Study C0524T09

		Golimumab	
	Placebo	50 mg	100 mg
Subjects Randomized	78	138	140
Subjects Treated	78	137*	140
Discontinued study agent through Week 14	2 (3%)	6 (4%)	3 (2%)
Adverse Event	1 (1%)	4 (3%)	3 (2%)
Unsatisfactory therapeutic effect	1 (1%)	0	0
Lost to follow-up	0	2 (1%)	0
Other	0	0	0
Discontinued study agent through Week 24	2 (3%)	9 (7%)	6 (4%)
Adverse Event	1 (1%)	4 (3%)	4 (3%)
Unsatisfactory therapeutic effect	1 (1%)	1 (1%)	0
Lost to follow-up	0	2 (1%)	0
Other	0	2 (1%)	2 (1%)
Terminated Study Participation through Week 24	2 (3%)	6 (4%)	2 (1%)
Withdraw Consent	1 (1%)	1 (1%)	1 (1%)
Lost to follow-up	0	2 (1%)	0
Other	1 (1%)	3 (2%)	1 (1%)
After Week 16 (Early Escape)**	37	154	165

Source: Clinical Study Report, for Week 14 Table 5 page 68 and for Week 24 Attachment 1.4 page 188 and Table 6 page 70
* One placebo subject (90031) was randomized but not treated
**Placebo → golimumab 50 mg; golimumab 50 mg → golimumab 100 mg; one subject randomized to placebo received golimumab 50 mg at Week 0.

The Applicant reported several protocol violations. A total of 14 randomized subjects (4%) did not meet selection criteria, 125 randomized subjects (35%) have deviations in study agent administration, and potentially 24 subjects have clinical supply issues (Table 16). The Applicant reported that between October 2006 and February 2007, they experienced significant issues associated with the availability of clinical supplies. The issues included difficulties in labeling, packaging, and distribution of sufficient quantities of study drug to meet the demands of these multiple studies. They reported that

> The impact of these issues was evaluated across all 5 studies and communicated to Health Authorities and investigative sites, including ECs/IRBs, on an ongoing basis during this period. As a result of the issues described above, disruptions in the study agent administration schedule occurred for some subjects in this study. To help affected study sites maintain the Protocol-specified dosing schedule during this period, the Applicant provided, wherever possible, a schedule to manage the study visits of each subject at a site based on the availability of study agent. The recommendation for rescheduling was based on the original subject visit schedule according to their date of randomization. To address the clinical supply availability

issues, Centocor reviewed internal processes, including study agent forecasting, and conducted vendor audits to determine sources contributing to the availability problem. Corrective actions were taken to ensure availability of study agent.

In order to ensure that none of these violations affected the efficacy results, re-analyses excluding these subjects were performed.

Table 16: Number of subjects (%) with Protocol Deviations – Study C0524T09

		Golimumab	
	Placebo	50 mg	100 mg
Subjects Randomized	78	138	140
Subjects who did not meet selection criteria †	5 (6%)	6 (4%)	3 (2%)
Subjects with study agent administration deviation‡	31 (40%)	45 (33%)	49 (35%)
Received incorrect study agent or dose	1 (1%)	0	1 (1%)
Missed an administration§	6 (8%)	8 (6%)	10 (7%)
Received scheduled administration outside protocol-specified window	27 (35%)	42 (31%)	41 (29%)
Mis-stratification (incorrect CRP values)	9 (12%)	12 (9%)	13 (9%)
Other Deviations**	3 (4%)	3 (2%)	4 (3%)
Study Agent Unblinding	1 (1%)	0	4 (3%)

† Based on the Table 7 of Clinical Study Report page 73
‡ Source: Clinical Study Report, Table 8 page 75
§ Re-analysis using Applicant's data; subjects who may have clinical supply issues are the same subjects who were classified as having missed an administration
** Deviation includes early escape and study agent storage

Demographic characteristics of subjects at baseline were generally well balanced across treatment groups (Appendix 13). The majority of subjects were men (72%) and Caucasian (74%). The median age was 39 years (range 18 to 83) and median weight was 75 kg (range 35 to 143 kg). Clinical disease characteristics at baseline, including duration of AS (Appendix 14), as well as baseline clinical disease characteristics (Appendix 15) and baseline clinical indices (Appendix 16) were also generally similar across the randomized groups. Subjects were stratified to treatment by screening CRP level and approximately two-third of the subjects in each treatment group had CRP level of $\leq$1.5 mg/dL at screening. The following are some of the observations reported by the Applicant.

- The placebo group had slightly longer number of years of inflammatory back pain and symptoms of spondyloarthropathy, as well as slightly longer duration of AS compared to golimumab groups.
- Disease activity (assessed by the subject on a 0 to 10 cm VAS included subject global assessment, total back pain and inflammation) and clinical indices (i.e. BASDAI, BASMI, BASFI, enthesitis, and Jenkins sleep) were generally well balanced across treatment group.

According to Dr. Brodsky, these observations are of no concern and do not affect the overall conclusion.

Both the SF-36 physical and mental component mean summary scores at baseline were in general similar across all treatment groups.

In terms of medications and/or therapies, the proportion of subjects who had taken prior medications such as DMARDs, systemic corticosteroids, and NSAIDs for AS were generally similar across all treatment groups.

3.1.2.2.2 Primary Efficacy Endpoint

The proportion of subjects achieving an ASAS 20 response at Week 14 in the combined golimumab group (60%) was greater than the proportion in the placebo group (22%), see Table 17. Pairwise comparisons between each golimumab dose groups and placebo demonstrated that the proportions of subjects achieving an ASAS 20 response in each of the golimumab groups were also greater than the proportion in the placebo group. Of note, the proportion of subjects achieving an ASAS 20 response in the golimumab 50 mg group (59%) is similar to that of the golimumab 100 mg group (60%). The ASAS 20 response was slightly higher for each golimumab dose group in the higher CRP stratum compared to the lower CRP stratum. There is a higher response in the golimumab 100 mg compared to golimumab 50 mg in the lower CRP stratum, while a lower response in the golimumab 100 mg compared to golimumab 50 mg in the higher stratum.

Table 17: Number of subjects (%) who achieved an ASAS 20 response at Week 14 stratified by screening CRP level – Study C0524T09 (Applicant's)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
ASAS 20				
n	78	138	140	278
Subjects in response	17 (21.8%)	82 (59.4%)	84 (60.0%)	166 (59.7%)
p-value		< 0.001	< 0.001	< 0.001
CRP (mg/L)≤ 1.5 mg/dL				
n	46	79	81	160
Subjects in response	10 (21.7%)	40 (50.6%)	43 (53.1%)	83 (51.9%)
CRP > 1.5 mg/dL				
n	32	59	59	118
Subjects in response	7 (21.9%)	42 (71.2%)	41 (69.5%)	83 (70.3%)

Source: Clinical Study Report, Table 16 page 104

As reported, incorrectly entered CRP values resulted in 34 subjects being assigned to the wrong stratum at randomization (see Table 16). In order to assess the impact of misstratification, the number of subjects who achieved ASAS 20 response at Week 14 by actual screening CRP levels is summarized in Table 18.

Table 18: Number of subjects (%) who achieved an ASAS 20 response at Week 14 stratified by **actual** screening CRP level – Study C0524T09 (Applicant's)

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Subjects randomized	78	138	140	278
ASAS 20				
n	78	138	140	278
Subjects in response	17 (21.8%)	82 (59.4%)	84 (60.0%)	166 (59.7%)
p-value		< 0.001	< 0.001	< 0.001
CRP (mg/L)≤ 1.5 mg/dL				
n	53	88	91	179
Subjects in response	12 (22.6%)	44 (50.0%)	49 (53.8%)	93 (52.0%)
CRP > 1.5 mg/dL				
n	25	49	48	97
Subjects in response	5 (20.0%)	37 (75.5%)	34 (70.8%)	71 (73.2%)

Source: Clinical Study Report, Table 17 page 105

The Applicant conducted three sensitivity analyses including three planned and two post-hoc analyses.

The following are the planned analyses:

1. Subjects who discontinued due to AEs were considered nonresponders.
2. Subjects with insufficient data to determine ASAS 20 response were considered nonresponders.
3. The analysis was based on observed data only

In the post hoc analyses,

4. Subjects who missed at least one administration of study agent for any reason prior to Week 14 were considered nonresponders
5. Subjects who missed at least one administration of study agent for any reason prior to Week 14 were excluded

The results are presented in Table 19. All five analyses supported the result of the primary endpoint analysis. The proportion of subjects achieving an ASAS 20 response in the combined golimumab group and in each of the individual golimumab groups in each analysis remained greater than the proportion in the placebo group.

Table 19: Number of subjects (%) who achieved an ACR 20 response at Week 14 (Sensitivity Analyses) – Study C0524T09 (Applicant's)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	78	138	140	278
ASAS 20 (Primary)	17 (22%)	82 (59%)	84 (60%)	166 (60%)
Sensitivity Analyses				
# 1 (AE as non-responder)	17 (22%)	82 (59%)	83 (59%)	165 (59%)
# 2 (Insufficient data as nonresponder)	17 (22%)	81 (59%)	84 (60%)	165 (59%)
# 3 (Observed data only)	17/78 (22%)	83/132 (60%)	84/137 (60%)	167/269 (62%)
# 4 (Missed at least one administration of study agent as nonresponders)	17 (22%)	80 (58%)	83 (59%)	163 (59%)
# 5 (Excludes subject with at least one missed administration of study agent)	17/72 (24%)	80/133 (60%)	83/136 (61%)	163/269 (61%)

Source: Clinical Study Report, Attachments 3.4 – 3.8, pages 353 – 357

A minor discrepancy was observed on the Applicant's efficacy datasets (Appendix 17). One placebo subject (ID 90334) should have been classified as 'ASAS 20 nonresponder' instead of 'ASAS 20 responder' since this subject did not have a baseline scores on global measure and the total pain measure. Although this did not affect the overall conclusion, the corrected result is reported and all the analyses that follow used this correct classification on subject 90334 (Table 20).

Table 20: Number of subjects (%) who achieved an ASAS 20 response at Week 14 (Re-Analyses) – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	78	138	140	278
ASAS 20 (Primary)	17 (22%)	81 (59%) <0.0001	84 (60%) <0.0001	165 (59%) <0.0001
CRP (≤1.5 mg/dL)* at Screening	46	79	81	160
ASAS 20	10 (22%)	40 (51%)	43 (53%)	83 (52%)
CRP (>1.5 mg/dL) at screening	32	59	59	118
ASAS 20	7 (22%)	41 (69%)	41 (69%)	82 (69%)
Actual CRP (≤1.5 mg/dL)* at Screening	53	88	91	179
ASAS 20	12 (23%)	43 (49%)	49 (54%)	92 (51%)
Actual CRP (>1.5 mg/dL) at Screening	25	49	48	97
ASAS 20	5 (20%)	37 (76%)	34 (71%)	71 (73%)

*Breslow-Day test of homogeneity across MTX strata was not significant (i.e. no interaction).

Additional analyses were conducted to assess the sensitivity of the primary analysis of ASAS 20 response by assigning non-responder status to subjects who discontinued study agent, as well as by excluding subjects with different protocol violations. The results are reported in Table 21. All five analyses supported the result of the primary endpoint analysis. The proportion of subjects achieving an ASAS 20 response in the combined golimumab group and in each of the individual golimumab groups in each analysis remained greater than the proportion in the placebo group.

Table 21: Number of subjects (%) who achieved an ASAS 20 response at Week 14 (Additional Analyses) – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	78	138	140	278
ASAS 20 (Primary)	17 (22%)	81 (59%) <0.0001	84 (60%) <0.0001	165 (59%) <0.0001
Sensitivity Analyses				
# 1 (Discontinued study agent as non-responder)	17 (22%)	81 (59%) <0.0001	83 (59%) <0.0001	164 (59%) <0.0001
# 2 (Exclude subject who did not meet selection criteria)	17/73 (23%)	79/132 (60%)	83/137 (61%)	162/269 (60%)
# 3 (exclude subject with study agent administration deviation)	10/47 (21%)	53/93 (57%)	57/91 (63%)	110/184 (60%)
# 4 (exclude subject with possible clinical supply issues)	17/72 (24%)	78/130 (60%)	80/130 (62%)	158/260 (61%)
# 5 (subject with any other protocol violations)	16/75 (21%)	80/135 (59%)	81/136 (60%)	161/271 (59%)

3.1.2.2.3 Secondary Endpoints

The Applicant conducted analyses of the secondary endpoints (see results below). Although all the results were in favor of golimumab dose groups, there are uncertainties with regards to some of these endpoints. According to Dr. Brodsky, information obtained when analyzing BASDAI is similar to that of ASAS 20, so reporting both results can be redundant. Like in the PsA study, multiple secondary endpoints are being considered (e.g. SF36) such that multiplicity is an issue. Although the results are reported in this review, I have strong reservations about including these results in the label.

ASAS 20 at Week 24

The proportion of subjects achieving an ASAS 20 response at Week 24 in the combined golimumab group (61%) and in each of the individual golimumab groups was greater for all comparisons than the proportion in the placebo group (23%). The last observed value prior to early escape for subjects in the placebo group and golimumab 50 mg group who entered early escape was used to calculate ASAS 20 response at Week 24.

In contrast to the ASAS 20 response at Week 14, the proportion of subjects achieving an ASAS 20 response at Week 24 is higher in the golimumab 100 mg group (61%) compared to golimumab 50 mg group (52%).

Table 22: Number of subjects (%) who achieved an ASAS 20 response at Week 24 – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
ASAS 20				
n	78	138	140	278
Subjects in response	18 (23.1%)	77 (55.8%)	92 (65.7%)	169 (60.8%)
p-value		< 0.001	< 0.001	< 0.001

RE24R[E_ASAS_5_A], 22JUN2007 18:11

Source: Clinical Study Report, Table 18, page 107

Additional analyses were conducted to assess the sensitivity of the analysis of ASAS 20 response at Week 24 that includes the following:

1. Subjects who entered early escape regardless of treatment group are considered 'nonresponders'.
2. The analysis is based on data reported at Week 24 regardless of subjects entering early escape.
3. Subjects who discontinued the study are considered 'nonresponder'. For subjects who entered early escape, the last observed value prior to early escape in the placebo group and golimumab 50 mg group was used to calculate ACR 20 response.

The results are presented in Table 23. All three analyses supported the result of the endpoint analysis at Week 24. The proportion of subjects achieving an ASAS 20 response in the combined golimumab group and in each of the individual golimumab groups in each analysis remained greater than the proportion in the placebo group. Of note, three subjects became non-responder when sensitivity # 3 was applied.

Table 23: Number of subjects (%) who achieved an ASAS 20 response at Week 24 (Sensitivity Analyses) – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	78	138	140	278
ASAS 20 at Week 24 (LOCF for early escape)	18 (23%)	77 (56%) <0.0001	92 (66%) <0.0001	169 (61%) <0.0001
Sensitivity Analyses				
ASAS 20 at Week 24 (from visit data)	18 (23%)	76 (55%)	92 (66%)	168 (60%)
# 1 (Early Escape as non-responder)	18 (23%)	77 (56%)	86 (61%)	163 (59%)
# 2 (Observed data at Week 24)	37/76 (49%)	80/130 (62%)	92/138 (67%)	172/268 (64%)
# 3 (Discontinue study agent as nonresponder)	18 (23%)	76 (55%)	90 (64%)	166(60%)

BASMI at Week 14

A summary of the change from baseline in BASMI at Week 14 is summarized below in Table 24 and Table 25. A negative/decreasing change from baseline is indicative of improvement in BASMI. The mean reduction (and percentage improvement) in BASMI at Week 14 was numerically greater for the golimumab treatment groups compared with placebo. A median change of 0 was noted for all groups.

Table 24: Summary of Change from Baseline in BASMI at Week 14; randomized subjects – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
Change from baseline				
n	78	138	140	278
Mean ± SD	-0.28 ± 1.015	-0.36 ± 1.112	-0.49 ± 1.296	-0.43 ± 1.208
Median	0.00	0.00	0.00	0.00
IQ range	(-1.00, 0.00)	(-1.00, 0.00)	(-1.00, 0.00)	(-1.00, 0.00)
Range	(-3.0, 2.0)	(-4.0, 3.0)	(-4.0, 3.0)	(-4.0, 3.0)
p-value		0.444	0.247	0.288

RE248:[S_BASM_4_A], 22JUN2007 18:12

Source: Clinical Study Report, Table 20, page 108

Table 25: Summary of Change from Baseline in BASMI at Week 14; randomized subjects – Study C0524T09 (Re-Analysis)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	78	138	140	278
Change from baseline (SD)	-0.3 (1.0)	-0.4 (1.2)	-0.5 (1.3)	-0.4 (1.2)
Percent Improvement from baseline (SD)	7.5 (34.3)	8.3 (50.4)	10.3 (46.2)	9.3 (48.3)

BASDAI at Week 14 and 24

The proportion of subjects achieving at least a 50% change from baseline in BASDAI at Week 14 in the golimumab 50 mg and in golimumab 100 mg groups was greater than in the placebo group. Similarly, the proportions of subjects achieving at least a 50% change from baseline at Week 24 was also greater in the combined golimumab group and in each of the individual groups than in the placebo group.

Table 26: Number of subjects who achieved at least a 50% improvement from baseline in BASDAI at Week 14 and at Week 24; randomized subjects – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
Week 14				
n	78	133	137	270
Subjects with improvement	12 (15.4%)	61 (45.9%)	56 (40.9%)	117 (43.3%)
p-value		< 0.001	< 0.001	< 0.001
Week 24				
n	75	130	138	268
Subjects with improvement	11 (14.7%)	66 (50.8%)	66 (47.8%)	132 (49.3%)
p-value		< 0.001	< 0.001	< 0.001

[illegible]

Source: Clinical Study Report, Table 24, page 113

ASAS 20 Core Components

A summary of the change from baseline in BASFI at Week 14 is shown in Table 27 and Table 28. A negative/decreasing change from baseline is indicative of improvement in BASFI.
Mean reduction in BASFI was numerically greater for the golimumab groups compared to the placebo group. Both golimumab groups also showed improvement over the placebo group.

Table 27: Summary of Change from Baseline in BASFI at Week 14; randomized subjects – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
Change from baseline				
n	78	138	140	278
Mean ± SD	0.026 ± 1.8179	-1.643 ± 2.0984	-1.603 ± 2.3261	-1.623 ± 2.2121
Median	0.095	-1.375	-1.495	-1.420
IQ range	(-1.050, 1.120)	(-3.130, -0.120)	(-2.985, -0.060)	(-3.070, -0.080)
Range	(-4.23, 4.54)	(-7.25, 3.95)	(-8.47, 5.06)	(-8.47, 5.06)
p-value		< 0.001	< 0.001	< 0.001

RE248:[E_BASF_4_A], 22JUN2007 19:12

Source: Clinical Study Report, Table 19, page 107

Table 28: Summary of Change from Baseline in BASFI at Week 14; randomized subjects – Study C0524T09 (Re-Analysis)

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized	78	138	140	278
Change from baseline (SD)	-0.04 (1.8)	-1.7 (2.1)	-1.6 (2.3)	-1.6 (2.2)
Percent Improvement from baseline (SD)	7.5 (64.8)	34.1 (55.1)	17.7 (131.8)	25.8 (101.7)

The change from baseline in subject global assessment of disease activity (an ASAS 20 component) is summarized in Table 29 and in Appendix 18 (by visit). A negative/decreasing change from baseline is indicative of improvement in subject global assessment. Mean reduction in subject global assessment of disease activity was higher for the golimumab group compared the placebo group at Weeks 14 and 24. Both golimumab groups also showed improvement over the placebo group.

Table 29: Summary of Change from Baseline in Subject Global at Disease Activity Scores at Week 14 and at Week 24; randomized subjects – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized – Week 14*	78	132	137	269
Change from baseline (SD)	-1.0 (2.5)	-2.9 (2.8)	-3.0 (3.1)	-3.0 (3.0)
Percent Improvement from baseline (SD)	8.9 (51.8)	43.7 (40.4)	43.4 (42.7)	43.5 (41.5)
Subjects Randomized – Week 24*	75	129	138	267
Change from baseline (SD)	-2.5 (2.9)	-3.2 (2.8)	-3.3 (3.3)	-3.3 (3.1)
Percent Improvement from baseline (SD)	32.5 (47.8)	47.7 (39.3)	47.4 (43.0)	47.6 (41.2)

*available data

The change from baseline in subject's assessment of total back pain (an ASAS 20 component) is summarized in Table 30 and in Appendix 19 (by visit). A negative/decreasing change from baseline is indicative of improvement in subject's assessment of total back pain. Mean reduction in subject's assessment of total back pain was higher for the golimumab group compared the placebo group at Weeks 14 and 24. Both golimumab groups also showed improvement over the placebo group.

Table 30: Summary of Change from Baseline in Subject's Assessment of Total Back Pain at Week 14 and at Week 24; randomized subjects – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized – Week 14*	78	132	137	269
Change from baseline (SD)	-1.4 (2.7)	-3.2 (2.9)	-3.5 (3.0)	-3.3 (3.0)
Percent Improvement from baseline (SD)	17.7 (38.4)	44.9 (40.5)	46.0 (39.4)	45.7 (39.8)
Subjects Randomized – Week 24*	75	129	138	267
Change from baseline (SD)	-2.9 (3.0)	-3.5 (3.0)	-3.8 (3.2)	-3.7 (3.1)
Percent Improvement from baseline (SD)	36.8 (40.5)	49.0 (41.6)	50.3 (40.9)	49.7 (41.2)

*available data

The change from baseline in inflammation (overall morning stiffness), an ASAS 20 component at Week 14 and Week 24 is summarized in Table 31 and in Appendix 20. The change from baseline in inflammation and percentage improvement were greater in the combined golimumab group as well as in each of the individual golimumab groups than in the placebo group at Weeks 14 and 24.

Table 31: Summary of Change from Baseline in Inflammation (Overall Morning Stiffness) at Week 14 and at Week 24; randomized subjects – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects Randomized – Week 14*	78	133	137	270
Change from baseline (SD)	-1.0 (2.4)	-3.4 (2.8)	-3.4 (3.0)	-3.4 (2.9)
Percent Improvement from baseline (SD)	-20.1 (294.4)	50.8 (40.3)	34.8 (141.7)	42.7 (104.9)
Subjects Randomized – Week 24*	75	130	138	268
Change from baseline (SD)	-2.3 (2.5)	-3.6 (2.7)	-3.6 (3.3)	-3.6 (3.0)
Percent Improvement from baseline (SD)	-8.2 (383.2)	55.0 (37.1)	33.7 (193.7)	44.0 (141.5)

*available data

3.1.2.2.4 Additional Analyses to Support the Primary Efficacy Analysis

ASAS 40 at Week 14 and Week 24

An ASAS 40 response is defined as 40% improvement in 3 of the 4 ASAS domains with an absolute improvement of at least 2 cm on a 0 to 10 cm scale, and no deterioration in the remaining domain.

The proportions of subjects achieving an ASAS 40 response at both Week 14 and Week 24 was greater in the combined golimumab group and in each of the individual groups than in the placebo group.

Like in ASAS 20 response, a minor discrepancy was observed in the Applicant's efficacy datasets (Appendix 17). One placebo subject (ID 90334) should have been classified as 'ASAS40 nonresponder' instead of 'ASAS40 responder' since this subject did not have a baseline scores on global measure and the total pain measure. This did not affect the overall conclusion.

Table 32: Number of subjects (%) who achieved an ASAS40 response at Week 14 and at Week 24 – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
ASAS 40				
Week 14				
n	78	138	140	278
Subjects in response	12 (15.4%)	62 (44.9%)	69 (49.3%)	131 (47.1%)
p-value		< 0.001	< 0.001	< 0.001
Week 24				
n	78	138	140	278
Subjects in response	12 (15.4%)	60 (43.5%)	76 (54.3%)	136 (48.9%)
p-value		< 0.001	< 0.001	< 0.001

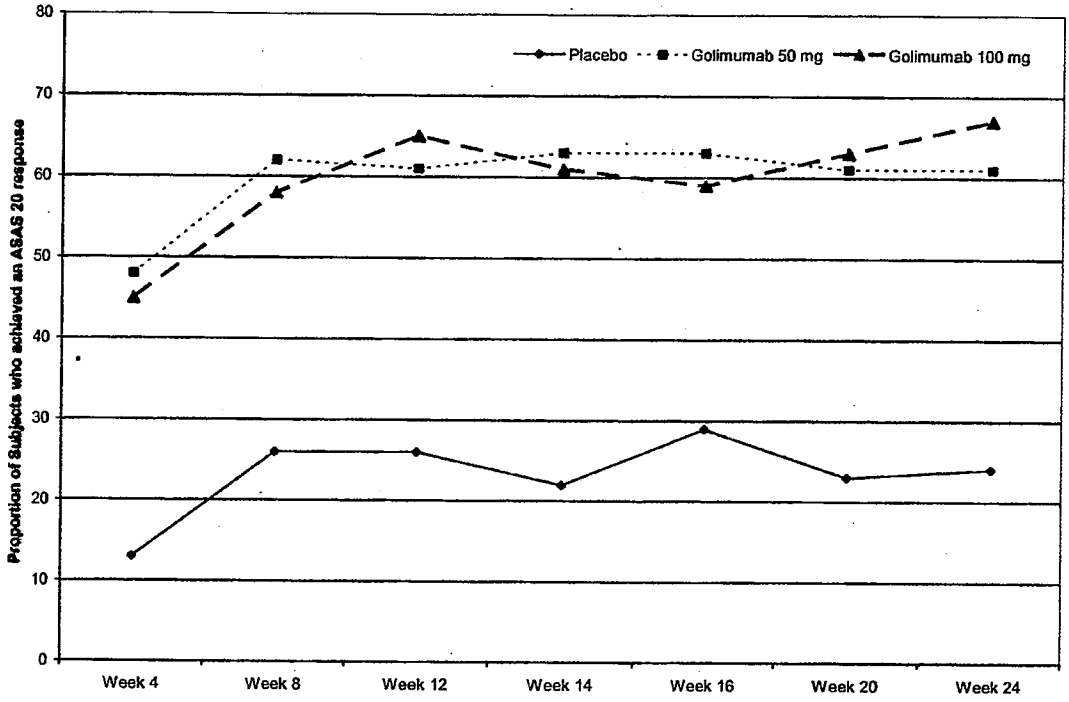
Source: Clinical Study Report, Table 23, page 111

ASAS 20 over time

The proportions of subjects with an ASAS 20 response based on available data at weeks 4, 8, 12, 14, 16, 20 and 24 are presented in Figure 12 and Appendix 21. The analysis applied the early escape rule. When subjects who discontinue study agent are classified as non-responder, the overall conclusion is generally similar.

By Week 4, there was a greater proportion of ASAS 20 responder in each of the individual golimumab groups than in the placebo group. There is no remarkable difference in the proportion of responders between golimumab 50 mg and golimumab 100 mg.

Figure 12: Proportion of ASAS 20 responders over time



Maintenance of Effect

An alternate way to view the treatment effect over time is to explore those subjects who responded to treatment at Week 24, using the ASAS 20 responder criteria. In the following two graphs (Figure 13 and Figure 14), we examined when these subjects started to respond to treatment and how often do they respond to the treatment. In some cases, subjects may respond early and then respond late again while some respond all throughout the study. In Figure 13, we assume that a subject who responded will respond up to the end of the study. Therefore the x-axis shows the week the subject started to respond, and the y-axis shows the proportion of subjects who are classified as ASAS 20 responder at that timepoint. In Figure 14, since there are a total of 6 study visits, the x-axis corresponds to the frequency of visits the subject had an ASAS 20 response and the y-axis shows the proportion of subjects who are classified as ASAS 20 responder. In general, each subject has a minimum of one visit that the subject is classified as ASAS 20 responder (at Week 24). A subject could be responding in all visits, therefore will be in the '>6' category; or a subject could be responding in 6 out of 7 visits and will be in the '>5' category.

A total of 186 subjects were classified as ASAS 20 responder at Week 24 using available data applying early escape rule and treatment failure rule. Among these responders, there is evidence that most subjects receiving golimumab 50 mg or golimumab 100 mg achieved the level of response (i.e. ASAS 20) as early as Week 4 (Figure 13). It appears the number of responders continue to increase through Week 12 and starts to plateau after that. In terms of maintenance, more than 80% of subjects in both golimumab groups who responded at Week 24 were responders at least 5 out of the 7 visits (Figure 14).

Figure 13: Start Time of ASAS 20 Responders– Study C0524T09

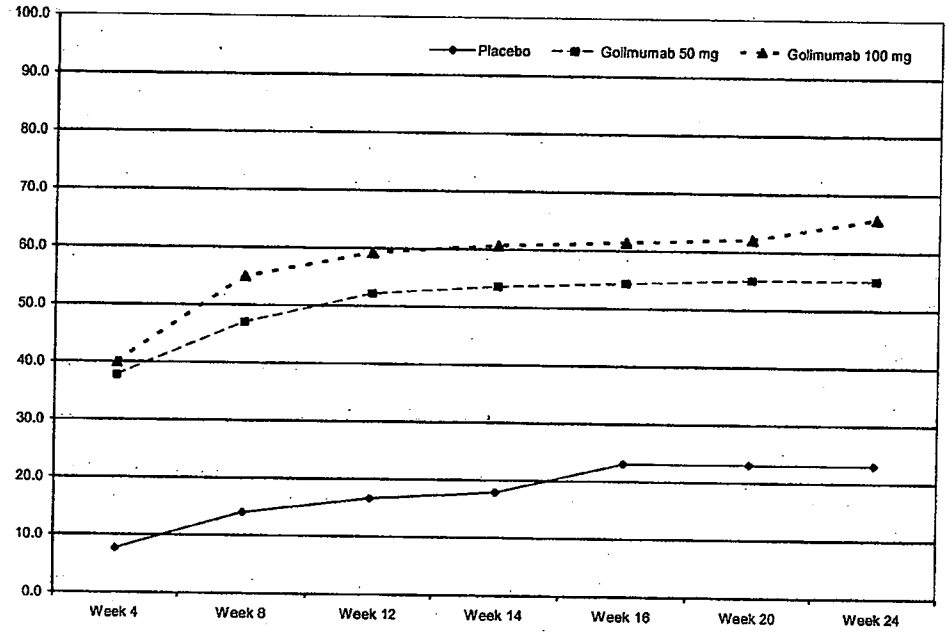
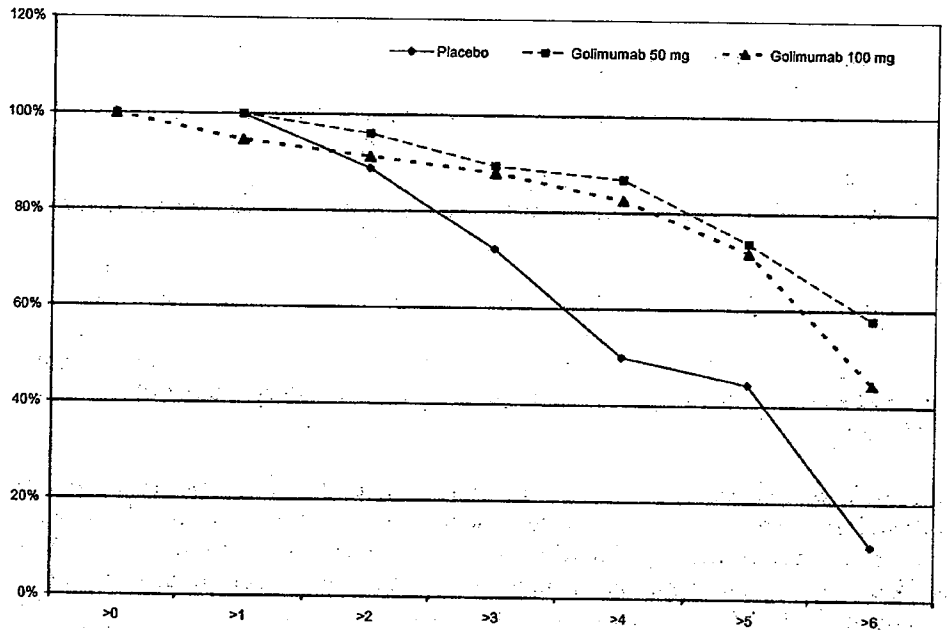


Figure 14: Frequency of Responses among Subjects Classified as ASAS 20 Responders– Study C0524T09



3.1.2.2.5 Findings in Subgroups and Special Population

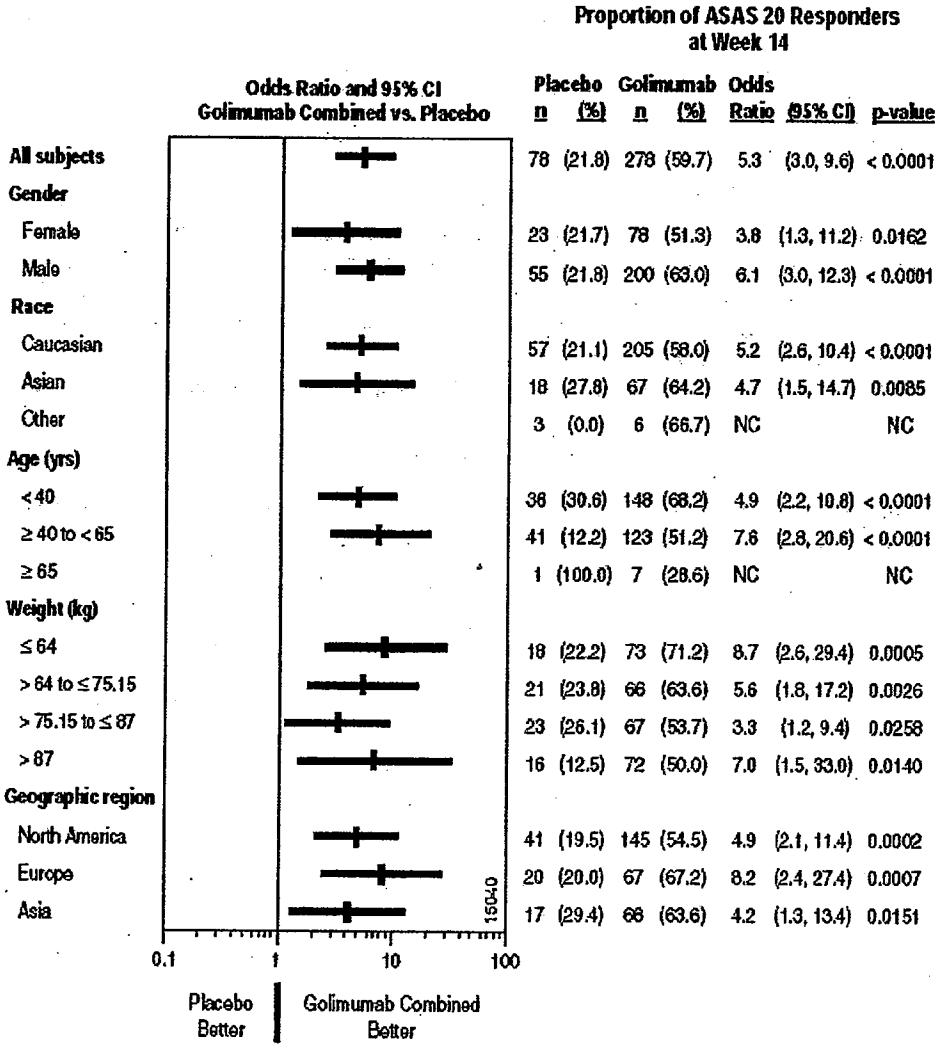
The Applicant conducted subgroup analyses on the primary endpoint (i.e. ASAS 20 at Week 14). In their report, they calculated the odds ratios and corresponding CIs in subgroups for demographic and baseline disease characteristics and the use of certain medications. They used the following criteria to interpret the results:

> An odds ratio greater than 1 corresponds to an observed ASAS 20 response rate that was greater with golimumab than with placebo. Subgroup odds ratios with CIs that overlap the CI for all subjects indicate treatment effect within the subgroup was consistent with the treatment effect observed in the overall study population.

The following figures (Figure 15 and Figure 16) are the odds ratios and 95% CIs for ASAS 20 response by subgroup based on demographic characteristics. Treatment benefits with golimumab (combined or individually) versus placebo appear to be consistent in almost all subgroups except perhaps on weight when individual golimumab dose is compared to placebo. The 95% confidence interval for the odds ratios contains the null in weight quartile >87 kg when golimumab 50 mg group is compared to placebo and in weight quartile >75.15 to ≤ 87 kg when golimumab 100 mg is compared to placebo. The limited statistical power due to the small size of the subgroups in the subgroup analyses by dose should be borne in mind.

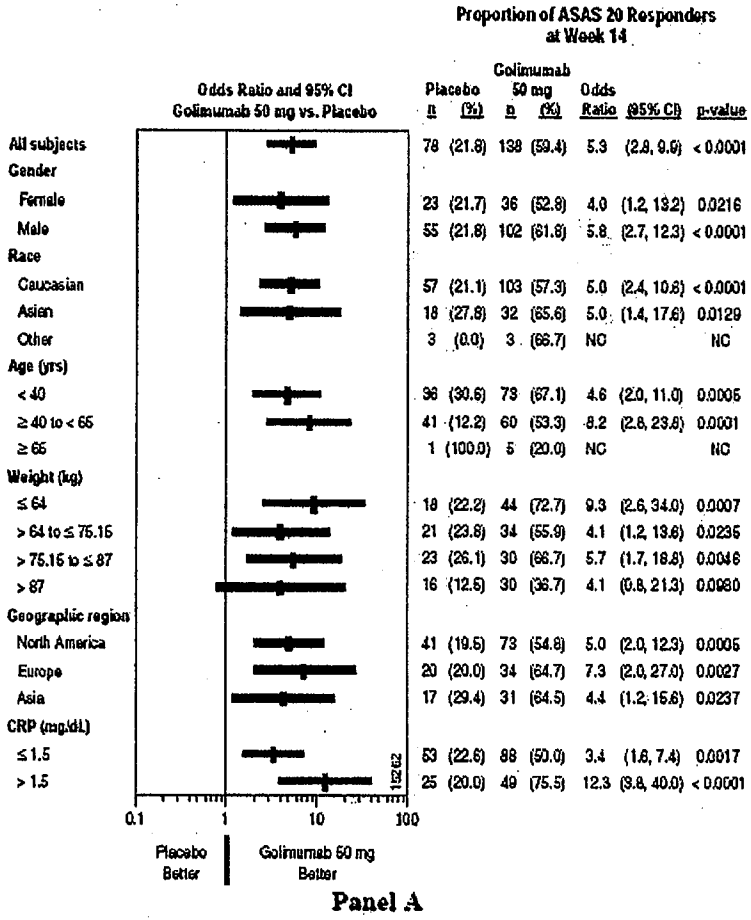
In Appendix 22 and Appendix 23, subgroups based on baseline disease and clinical characteristics, and baseline medication and prior therapies for AS are presented. Like the demographic characteristics, treatment benefit with golimumab versus placebo appears to be consistent in all subgroups.

Figure 15: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ASAS 20 response at Week 14 in the golimumab **combined** group versus the placebo group for subgroups defined by demographic characteristics; randomized subjects

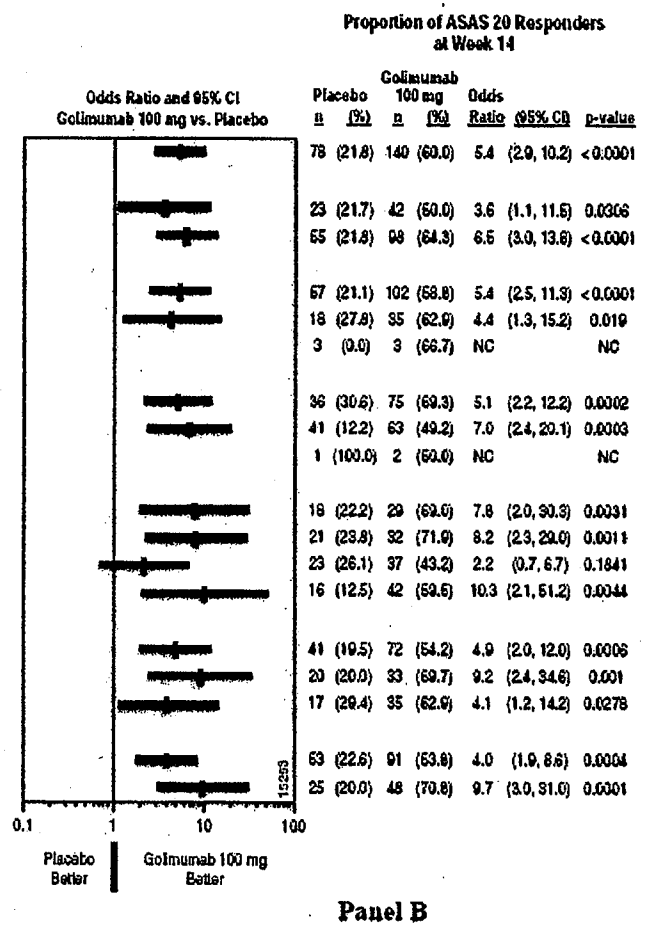


Source: Clinical Study Report, Attachment 3.58 page 419

Figure 16: Odds ratio (vertical bars) and 95 % confidence intervals (horizontal bars) for comparing proportion of subjects who achieved ASAS 20 response at Week 14 in the **golimumab 50 mg group or golimumab 100 mg group** versus the placebo group for selected subgroups; randomized subjects



Panel A



Panel B

Source: Clinical Study Report, Figure 9 page 128

3.1.2.2.6 Efficacy Conclusion

In Study C0524T09, there is evidence that golimumab 50 mg and golimumab 100 mg administered SC every four (q4) weeks in subjects with active AS (despite current or previous DMARD or NSAID therapy and had not been treated previously with anti-TNFα therapy) reduces signs and symptoms of AS. This is based on the result from the analysis of the primary endpoint (i.e. ASAS 20 at Week 14). The evidence is also supported by the results from the analyses of other endpoints (e.g. ASAS 40 and all the ASAS components), as well as result from the analysis of the primary endpoint at Week 24.

The ASAS 20 response was slightly higher for each golimumab dose group in the higher CRP stratum compared to the lower CRP stratum. There is also a slightly higher response in the golimumab 100 mg compared to golimumab 50 mg in the lower CRP stratum, while a slightly lower response in the golimumab 100 mg compared to golimumab 50 mg in the higher stratum.

Like in the PsA Study, although no formal analysis was conducted to compare the two golimumab doses, numerically, there is no difference in the proportion of ASAS 20 responders between the two doses at Week 14. There is no treatment benefit with the 100 mg dose compared to the golimumab 50 mg dose at this time. This evidence is also supported by the results from the analyses of other endpoints (e.g. ASAS 40 and all the ASAS components) at Week 14. In contrast, there is some evidence that at Week 24, there is higher proportion of ASAS 20 responder in the golimumab 100 mg group compared to golimumab 50 mg. I refer the reader to Dr. Brodsky review on the benefit-risk profile of these doses. Like the PsA study, my recommendation is that patient should be administered with golimumab 50 mg QD every four weeks at least as a starting dose.

When responder status throughout the 24 week treatment period (assessment starts at Week 4) were assessed, there is evidence that most subjects receiving golimumab 50 mg or golimumab 100 mg achieved the level of response (i.e. ACR 20) as early as Week 4. In the 24-week treatment period which comprised of 7 visits, more than 80% of subjects in both golimumab groups who responded at Week 24 were responders at least 5 out of the 7 visits. More than 40% in the golimumab 100 mg group and more than 55% in the golimumab 50 mg group who responded at Week 24 maintained their response in all seven visits (starting at Week 4). Therefore, there is evidence that subjects taking golimumab 50 mg maintained their responder status throughout the treatment period.

Secondary endpoints were also analyzed. These include BASDAI and SF36-PCS to measure disease burden. Although the results from the analyses of these endpoints are in favor of golimumab over placebo, I have strong reservations about including these results in the label for the following reasons:

1. According to Dr. Brodsky, information obtained when analyzing BASDAI is similar to that of ASAS 20, so reporting both results can be redundant.
2. Multiple secondary endpoints are being considered (e.g. SF36) such that multiplicity is an issue.

3.2 EVALUATION OF SAFETY

Dr. Eric Brodsky reviewed the safety of golimumab in detail. The reader is referred to Dr. Brodsky's review for information regarding the adverse event profile.

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

Subgroup findings for the PsA study (Study C0524T08) and the AS study (Study C0524T09) are presented in Section 3.1.1.2.5 and in Section 3.1.2.2.5, respectively.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

During my review of the PsA and AS studies, I found no issues that that could not be resolved by recoding and/or re-analyzing the data. Although various discrepancies between the raw and derived datasets were observed, all of these discrepancies were found not to affect the overall conclusion.

An example is the randomization strategy (i.e. minimization with biased coin assignment) the Applicant applied to allocate patients. This strategy may result in the predictability of randomization sequences and may potentially undermine the applicability of conventional statistical tests (e.g. Cochran-Mantel Haenszel test).

The Applicant addressed the concern by conducting re-randomization tests for both studies. The results obtained by these tests were similar to the ones obtained by using the conventional CMH test when adaptive randomization was used.

Summary of efficacy results for the PsA (Study C0524T08) and the AS study (Study C0524T09) are presented in Section 3.1.1.2.6 and in Section 3.1.2.2.6, respectively.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The Applicant, Centocor Incorporated, seeks to market SIMPONI for the treatment of adult subjects (18 years or older) with active rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The focus of this statistical review is on the Psoriatric Arthritis study and the Ankolysing Spondylitis studies. Dr. Jonathan Norton is the primary statistical reviewer for the Rheumatoid Arthritis studies. Dr. Eric Brodsky reviewed the safety of golimumab in detail, as well as the benefit-risk profile of golimumab.

The focus of this statistical review is on the Psoriatric Arthritis and the Ankolysing Spondylitis studies. Dr. Jonathan Norton is the primary statistical reviewer for the Rheumatoid Arthritis studies.

Overall, there is statistical support in favor of golimumab 50 mg or golimumab 100 mg in reducing signs and symptoms of PsA (based on Study C0524T08) and AS (based on Study C0524T09). This is based on the result from the analysis of the primary endpoint (i.e. ACR 20 at Week 14 in Study C0524T08 and ASAS 20 at Week 14 in Study C0524T09).

Although no formal analysis was conducted to compare the golimumab dose groups, numerically, there is generally no difference in the proportion of responders (ACR 20 or ASAS 20) between golimumab 50 mg and golimumab 100 mg at Week 14. However at Week 24, a slightly higher proportion of ACR 20 responders and ASAS 20 responders in the golimumab 100 mg group were observed compared to golimumab 50 mg. In conclusion since there was no added benefit of golimumab 100 mg at Week 14, I agree with the Applicant's recommendation that patient should be administered golimumab 50 mg QD every four weeks.

Based on the analysis of Week 24 responders, there is evidence that most subjects receiving golimumab 50 mg or golimumab 100 mg achieved the level of response as early as Week 4 in both PsA and AS studies. Thirty percent of subjects in the PsA study and more than 50% of subjects in the AS study maintained their response in all visits (starting at Week 4). Therefore, there is evidence that subjects taking golimumab 50 mg maintained their responder status throughout the treatment period.

Secondary endpoints were also analyzed. Although the results from the analyses of these endpoints are in favor of golimumab over placebo, I recommend that the results from the analyses of the endpoints that are not related to the indication (e.g. PASI 75 in the PsA) or those that do not provide additional information (e.g. BASDAI in the AS study) be excluded in the label.

6 LABELLING

[redacted]

b(4)

7 APPENDIX

Appendix 1: Definitions of the terms used

Continuing Study Agent: Subjects who did not discontinue study agent before Week 24.

Discontinued Study Agent:

- Subjects who discontinued study agent before Week 24 but were being followed for safety at the time of database lock.
- Subjects who discontinued study agent before Week 24 and had completed safety follow-up before database lock (considered to have ended participation).
- Subjects who terminated participation in the study and did not return for additional safety procedures (considered to have ended participation).

Appendix 2: Summary of Demographics at Baseline – Randomized Subjects (Study C0524T08

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined	Total
Subjects randomized	113	146	146	292	405
Sex					
n	113	146	146	292	405
Male	69 (61.1%)	89 (61.0%)	86 (58.9%)	175 (59.9%)	244 (60.2%)
Female	44 (38.9%)	57 (39.0%)	60 (41.1%)	117 (40.1%)	161 (39.8%)
Race					
n	113	146	146	292	405
Caucasian	110 (97.3%)	141 (96.6%)	142 (97.3%)	283 (96.9%)	393 (97.0%)
Black	1 (0.9%)	0 (0.0%)	1 (0.7%)	1 (0.3%)	2 (0.5%)
Asian	1 (0.9%)	3 (2.1%)	3 (2.1%)	6 (2.1%)	7 (1.7%)
Other	1 (0.9%)	2 (1.4%)	0 (0.0%)	2 (0.7%)	3 (0.7%)
Age (yrs)					
n	113	146	146	292	405
Mean ± SD	47.0 ± 10.56	45.7 ± 10.70	48.2 ± 10.93	47.0 ± 10.87	47.0 ± 10.77
Median	47.0	44.0	50.0	47.0	47.0
IQ range	(40.0, 54.0)	(38.0, 54.0)	(39.0, 56.0)	(38.5, 55.0)	(39.0, 55.0)
Range	(24, 70)	(23, 78)	(20, 77)	(20, 78)	(20, 78)
Weight (kg)					
n	113	146	146	292	405
Mean ± SD	85.72 ± 18.138	83.50 ± 20.787	86.53 ± 19.039	85.01 ± 19.956	85.21 ± 19.446
Median	86.30	80.70	84.60	82.90	84.00
IQ range	(70.00, 96.80)	(69.30, 94.30)	(71.60, 99.20)	(70.15, 96.90)	(70.00, 96.80)
Range	(52.3, 136.0)	(43.0, 191.0)	(50.0, 144.1)	(43.0, 191.0)	(43.0, 191.0)
Height (cm)					
n	113	146	146	292	405
Mean ± SD	170.5 ± 9.48	169.6 ± 8.64	169.2 ± 9.65	169.4 ± 9.14	169.7 ± 9.24
Median	172.0	170.1	169.5	170.0	170.0
IQ range	(164.5, 176.0)	(163.0, 175.0)	(162.0, 176.0)	(162.8, 175.2)	(163.0, 176.0)
Range	(144, 198)	(149, 194)	(145, 192)	(145, 194)	(144, 198)

Source: Clinical Study Report, Table 12, page 87

Appendix 3: Summary of Baseline Clinical Disease Characteristics – Randomized Subjects (Study C0524T08

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Subjects randomized	113	146	146	292
PsA subtypes				
n	113	146	146	292
DIP joint arthritis	16 (14.2%)	24 (16.4%)	22 (15.1%)	46 (15.8%)
Arthritis mutilans	0 (0.0%)	2 (1.4%)	1 (0.7%)	3 (1.0%)
Asymmetric peripheral arthritis	27 (23.9%)	44 (30.1%)	49 (33.6%)	93 (31.8%)
Polyarticular arthritis with no rheumatoid nodules	58 (51.3%)	62 (42.5%)	56 (38.4%)	118 (40.4%)
Spondylitis with peripheral arthritis	12 (10.6%)	14 (9.6%)	18 (12.3%)	32 (11.0%)
PsA duration (yrs)				
n	113	146	146	292
Mean ± SD	7.64 ± 7.943	7.23 ± 6.807	7.70 ± 7.792	7.47 ± 7.308
Median	5.10	5.00	5.50	5.15
IQ range	(1.80, 10.20)	(1.80, 10.60)	(1.90, 10.20)	(1.85, 10.35)
Range	(0.1, 39.2)	(0.3, 31.0)	(0.4, 44.5)	(0.3, 44.5)
Psoriasis duration (yrs)				
n	113	146	146	292
Mean ± SD	18.98 ± 12.928	17.67 ± 11.887	18.40 ± 12.682	18.03 ± 12.275
Median	17.50	15.90	17.35	16.40
IQ range	(9.30, 25.70)	(8.90, 24.30)	(8.20, 26.10)	(8.25, 25.60)
Range	(0.5, 64.4)	(0.6, 58.5)	(0.2, 49.0)	(0.2, 58.5)
Percent BSA affected with psoriasis				
n	113	146	146	292
Subjects with < 3% BSA	34 (30.1%)	37 (25.3%)	38 (26.0%)	75 (25.7%)
Subjects with ≥ 3% BSA	79 (69.9%)	109 (74.7%)	108 (74.0%)	217 (74.3%)
Current MTX usage				
n	113	146	146	292
Subjects taking MTX	54 (47.8%)	71 (48.6%)	69 (47.3%)	140 (47.9%)
Subjects not taking MTX	59 (52.2%)	75 (51.4%)	77 (52.7%)	152 (52.1%)

Source: Clinical Study Report, Table 13, page 89.

Appendix 4: Baseline Disease Characteristics of PsA for ACR Core Set of Measurements - Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Number of swollen joints (0-66)				
n	113	146	146	292
Mean ± SD	13.4 ± 9.78	14.1 ± 11.40	12.0 ± 8.45	13.0 ± 10.07
Median	10.0	11.0	9.5	10.0
IQ range	(6.0, 18.0)	(7.0, 17.0)	(6.0, 14.0)	(6.0, 15.0)
Range	(3, 54)	(3, 55)	(3, 41)	(3, 55)
Number of tender joints (0-68)				
n	113	146	146	292
Mean ± SD	21.9 ± 14.68	24.0 ± 17.06	22.5 ± 15.71	23.3 ± 16.39
Median	18.0	19.0	18.0	18.5
IQ range	(11.0, 30.0)	(10.0, 33.0)	(10.0, 29.0)	(10.0, 32.0)
Range	(3, 68)	(3, 68)	(3, 66)	(3, 68)
Patient's assessment of pain (VAS; 0-10 cm)				
n	110	144	143	287
Mean ± SD	5.42 ± 2.311	5.61 ± 2.491	5.62 ± 2.253	5.62 ± 2.371
Median	5.40	5.75	5.60	5.70
IQ range	(3.10, 7.50)	(4.00, 7.40)	(4.20, 7.50)	(4.10, 7.40)
Range	(0.7, 9.4)	(0.2, 10.0)	(0.4, 9.9)	(0.2, 10.0)
Patient's global assessment of disease activity (VAS; 0-10 cm)				
n	110	144	143	287
Mean ± SD	5.08 ± 2.334	5.39 ± 2.434	5.38 ± 2.251	5.39 ± 2.340
Median	5.15	5.15	5.30	5.30
IQ range	(3.70, 6.90)	(3.60, 6.95)	(4.20, 7.10)	(3.90, 7.00)
Range	(0.0, 9.8)	(0.1, 10.0)	(0.2, 10.0)	(0.1, 10.0)
Physician's global assessment of disease activity (VAS; 0-10 cm)				
n	113	146	146	292
Mean ± SD	5.48 ± 1.669	5.44 ± 1.844	5.28 ± 1.752	5.36 ± 1.797
Median	5.20	5.40	5.20	5.30
IQ range	(4.40, 6.80)	(4.10, 7.00)	(4.10, 6.50)	(4.10, 6.80)
Range	(1.6, 8.9)	(1.7, 9.6)	(1.2, 10.0)	(1.2, 10.0)

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
HAQ score (0-3)				
n	113	145	145	290
Mean ± SD	1.0265 ± 0.54753	0.9802 ± 0.64813	1.0509 ± 0.62300	1.0155 ± 0.63557
Median	1.0000	1.0000	1.1250	1.0000
IQ range	(0.6250, 1.3750)	(0.5000, 1.3750)	(0.5000, 1.5000)	(0.5000, 1.5000)
Range	(0.000, 2.375)	(0.000, 2.750)	(0.000, 2.875)	(0.000, 2.875)
CRP (mg/dL)				
n	112	145	145	290
Mean ± SD	1.26 ± 1.555	1.31 ± 1.617	1.38 ± 1.782	1.34 ± 1.699
Median	0.60	0.60	0.60	0.60
IQ range	(0.30, 1.30)	(0.30, 1.60)	(0.30, 1.70)	(0.30, 1.60)
Range	(0.3, 8.1)	(0.3, 8.1)	(0.3, 12.1)	(0.3, 12.1)

Source: Clinical Study Report, Table 14, page 90-91

Appendix 5: Baseline Disease Characteristics of PsA for measurements other than ACR core set – Study C0524T08

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Subjects randomized	113	146	146	292
Patient's global assessment of disease (Likert) (1-5)				
n	110	144	144	288
Mean ± SD	3.2 ± 0.68	3.4 ± 0.79	3.3 ± 0.76	3.3 ± 0.77
Median	3.0	3.0	3.0	3.0
IQ range	(3.0, 4.0)	(3.0, 4.0)	(3.0, 4.0)	(3.0, 4.0)
Range	(2, 5)	(2, 5)	(2, 5)	(2, 5)
Physician's global assessment of disease (Likert) (1-5)				
n	113	146	146	292
Mean ± SD	3.2 ± 0.66	3.3 ± 0.64	3.1 ± 0.59	3.2 ± 0.62
Median	3.0	3.0	3.0	3.0
IQ range	(3.0, 4.0)	(3.0, 4.0)	(3.0, 3.0)	(3.0, 4.0)
Range	(2, 5)	(2, 5)	(2, 5)	(2, 5)
Tender joint score (0-3 x 68)				
n	113	146	146	292
Mean ± SD	31.3 ± 25.63	35.4 ± 29.88	31.3 ± 25.57	33.4 ± 27.83
Median	24.0	26.0	23.5	24.0
IQ range	(14.0, 38.0)	(14.0, 43.0)	(14.0, 37.0)	(14.0, 39.0)
Range	(3, 167)	(3, 121)	(3, 136)	(3, 136)
Swollen joint score (0-3 x 66)				
n	113	146	146	292
Mean ± SD	17.4 ± 14.59	18.0 ± 15.09	14.7 ± 10.01	16.3 ± 12.89
Median	16.0	13.0	11.0	13.0
IQ range	(8.0, 20.0)	(8.0, 21.0)	(7.0, 18.0)	(8.0, 19.0)
Range	(3, 96)	(3, 92)	(3, 45)	(3, 92)
Number of swollen joints (0-28)[a]				
n	113	146	146	292
Mean ± SD	7.8 ± 5.87	7.7 ± 5.68	6.9 ± 4.70	7.3 ± 5.22
Median	6.0	6.0	6.0	6.0
IQ range	(4.0, 11.0)	(4.0, 10.0)	(4.0, 9.0)	(4.0, 10.0)
Range	(0, 24)	(0, 25)	(0, 24)	(0, 25)

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Number of tender joints (0-28)[a]				
n	113	146	146	292
Mean ± SD	10.1 ± 6.91	11.0 ± 7.75	10.3 ± 7.29	10.6 ± 7.52
Median	9.0	9.0	9.0	9.0
IQ range	(4.0, 14.0)	(5.0, 17.0)	(5.0, 15.0)	(5.0, 15.5)
Range	(0, 28)	(0, 28)	(0, 28)	(0, 28)
DAS 28 score[a]				
n	109	143	142	285
Mean ± SD	4.307 ± 0.9876	4.414 ± 1.0612	4.335 ± 1.0112	4.374 ± 1.0355
Median	4.218	4.422	4.233	4.309
IQ range	(3.708, 4.965)	(3.667, 4.927)	(3.547, 5.053)	(3.619, 5.032)
Range	(1.75, 6.68)	(2.19, 6.91)	(1.99, 6.63)	(1.99, 6.91)
Duration of morning stiffness (0-1440 min)				
n	113	146	145	291
Mean ± SD	131.1 ± 264.87	124.7 ± 262.31	117.8 ± 234.12	121.2 ± 248.26
Median	60.0	60.0	60.0	60.0
IQ range	(30.0, 120.0)	(30.0, 120.0)	(30.0, 120.0)	(30.0, 120.0)
Range	(0, 1440)	(0, 1440)	(0, 1440)	(0, 1440)
Number of subjects with digits with dactylitis	38 (33.6%)	50 (34.2%)	49 (33.6%)	99 (33.9%)
Dactylitis score (1-60)				
n	38	50	49	99
Mean ± SD	3.1 ± 2.07	6.3 ± 6.05	5.4 ± 6.68	5.8 ± 6.35
Median	2.0	4.5	4.0	4.0
IQ range	(2.0, 4.0)	(2.0, 8.0)	(2.0, 5.0)	(2.0, 7.0)
Range	(1, 10)	(1, 29)	(1, 30)	(1, 30)
Number of subjects with enthesitis[b]	88 (77.9%)	109 (74.7%)	115 (78.8%)	224 (76.7%)
Enthesitis score (1-15)[b]				
n	88	109	115	224
Mean ± SD	5.0 ± 4.08	5.7 ± 3.99	6.1 ± 4.13	5.9 ± 4.06
Median	4.0	4.0	5.0	5.0
IQ range	(2.0, 7.5)	(3.0, 8.0)	(3.0, 9.0)	(3.0, 9.0)
Range	(1, 15)	(1, 15)	(1, 15)	(1, 15)

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Target lesion score (0-12)				
n	113	146	146	292
Mean ± SD	6.1 ± 2.01	6.2 ± 2.12	6.3 ± 2.35	6.3 ± 2.24
Median	6.0	6.0	6.0	6.0
IQ range	(5.0, 7.0)	(5.0, 8.0)	(4.0, 8.0)	(4.0, 8.0)
Range	(2, 12)	(2, 12)	(1, 12)	(1, 12)
PASI score (0-72) in subjects with ≥ 3% BSA psoriasis skin involvement				
n	78	109	108	217
Mean ± SD	8.38 ± 7.382	9.75 ± 8.592	11.11 ± 9.497	10.43 ± 9.058
Median	6.15	7.50	7.60	7.50
IQ range	(3.90, 10.00)	(4.00, 13.40)	(4.60, 15.00)	(4.20, 14.30)
Range	(0.3, 40.6)	(0.3, 56.7)	(0.4, 51.0)	(0.3, 56.7)
Number of subjects with fingernail involvement	83 (73.5%)	95 (65.1%)	109 (74.7%)	204 (69.9%)
NAPSI score (1-8) of target fingernail				
n	83	95	109	204
Mean ± SD	4.43 ± 2.165	4.66 ± 2.196	4.60 ± 2.144	4.63 ± 2.163
Median	4.00	4.00	4.00	4.00
IQ range	(2.00, 6.00)	(3.00, 6.00)	(3.00, 6.00)	(3.00, 6.00)
Range	(1.0, 8.0)	(1.0, 8.0)	(1.0, 8.0)	(1.0, 8.0)
Number of fingernails involved (1-10)				
n	83	95	109	204
Mean ± SD	6.3 ± 3.40	6.7 ± 3.37	6.2 ± 3.43	6.5 ± 3.40
Median	6.0	8.0	6.0	7.0
IQ range	(3.0, 10.0)	(3.0, 10.0)	(3.0, 10.0)	(3.0, 10.0)
Range	(1, 10)	(1, 10)	(1, 10)	(1, 10)
Nail PGA				
n	83	95	109	204
Very severe	1 (1.2%)	3 (3.2%)	5 (4.6%)	8 (3.9%)
Severe	10 (12.0%)	16 (16.8%)	15 (13.8%)	31 (15.2%)
Moderate	29 (34.9%)	37 (38.9%)	35 (32.1%)	72 (35.3%)
Mild	43 (51.8%)	39 (41.1%)	54 (49.5%)	93 (45.6%)

[a] For DAS28 score, only 28 joints are evaluated for both tenderness and swelling.
[b] Based on modified MASES index.
[c] Based on subjects with enthesitis

Source: Clinical Study Report, Attachment 1.10, page 230 - 233

Appendix 6: Discrepancies in Study C0524T08

A minor discrepancy was observed in the Applicant's efficacy datasets (subjef.xpt and visra.xpt).

The file 'subjef.xpt' contains subject-level efficacy data, while the file 'visra.xpt' contains visit-level efficacy data. Both datasets contained the ACR 20 responder, ACR 50 responder and ACR 70 responder variables, as well as the derived-ACR index of improvement (ACRn) variable. This index is derived using the following rule:

> Derived ACRN is calculated as the minimum of the following 3 values:
> 1) Percent improvement in swollen joints
> 2) Percent improvement in tender joints
> 3) The median percent improvement of the additional 5 ACR components (subject's assessment of pain, subject's global assessment of disease activity, evaluator's global assessment of disease activity, standard HAQ, and CRP).
>
> Of note, the early escape,joint evaluability and zero divisor rules applied in the calculation.

In visra.xpt, when more than 2 components of the parameters making the 'median' are missing the ACRn is assigned a 'missing' value. When 1 or 2 components of the parameters making the 'median' are missing then the missing is replaced with the least amount of improvement (e.g. -99999) in the median calculation.

In contrast, when 1 or 2 components of the parameters making the 'median' are missing in 'subjef.xpt', it appears that the missing is replaced with the greatest amount of improvement (e.g. +99999) in the median calculation, such that the calculated 'median' from this approach is slightly different from the calculated 'median' from the approach used in 'visra.xpt'.

The following are the discrepancies found at Week 14:

Obs	SUBJID	TRTGRP	POP_EE	PAINPI	GDPTPI	GDEVPI	HAQPI	CRPPI	medfive
134	80031	golimumab 100 mg	No	.	.	-2.0	.	0.0	.
342	80092	golimumab 50 mg	No	3.2	11.5	-99999.0	-33.3	-16.7	-16.7
348	80093	golimumab 50 mg	No	-4.3	46.0	47.1	25.0	-99999.0	25.0
450	80121	placebo	No	76.5	70.0	13.9	0.0	0.0	13.9
1002	80245	golimumab 100 mg	No	17.2	36.5	13.2	-5.9	0.0	13.2
1036	80255	golimumab 50 mg	No	.	.	76.4	.	-83.8	.
1042	80256	golimumab 100 mg	No	.	.	22.7	.	40.0	.
1054	80262	golimumab 50 mg	No	63.9	87.0	100.0	-99999.0	0.0	63.9
1375	80332	golimumab 100 mg	Yes	-57.9	-314.3	58.3	0.0	-99999.0	-57.9
2213	80529	placebo	Yes	-99999.0	-99999.0	-15.6	-50.0	-92.3	-92.3
2219	80530	placebo	No	-99999.0	-99999.0	60.0	0.0	25.0	0.0
2243	80535	golimumab 50 mg	No	-99999.0	-99999.0	87.5	50.0	79.2	50.0
2273	80541	golimumab 50 mg	No	-99999.0	-99999.0	95.1	100.0	57.1	57.1
2285	80543	golimumab 100 mg	No	-99999.0	-99999.0	78.6	100.0	64.3	64.3
2309	80547	golimumab 100 mg	No	-99999.0	-99999.0	87.0	72.7	72.7	72.7

Obs	SJCPI	TJCPI	acrn	ACRNEE	ACRNW14	~~ACR20~~ACR 20W14	~~ACR20~~ACR 20	VISIT
134	0.0	24.0	.	.	0.0	No	No	Week 14
342	61.5	33.3	-16.7	-16.7	3.2	No	No	Week 14
348	30.8	33.3	25.0	25.0	30.8	Yes	Yes	Week 14

450	.	.	.	.	-175.0	No	No	Week 14
1002	40.0	5.8	5.8	5.8	0.0	No	No	Week 14
1036	-40.0	33.3	.	.	-40.0	No	No	Week 14
1042	75.0	42.9	.	.	-8.1	No		Week 14
1054	100.0	100.0	63.9	63.9	87.0	Yes	Yes	Week 14
1375	100.0	-41.7	-57.9	-57.9	-41.7	No	No	Week 14
2213	11.1	26.5	-92.3	-92.3	-26.9	No	No	Week 14
2219	71.4	66.7	0.0	0.0	60.0	Yes		Week 14
2243	77.8	89.5	50.0	50.0	77.8	Yes	Yes	Week 14
2273	88.9	95.5	57.1	57.1	88.5	Yes	Yes	Week 14
2285	85.7	84.6	64.3	64.3	82.7	Yes	Yes	Week 14
2309	77.8	78.8	72.7	72.7	77.8	Yes	Yes	Week 14

Other than discrepancy in the ACRn calculation, five subjects' responder statuses were also affected. Subject ID 80530 (placebo) should be an ACR 20, ACR 50 or ACR 70 'nonresponder'. Subject IDs 80262, 80535, 80541, and 80543 should be ACR 70 nonresponders.

Obs	SUBJID	TRTGRP	POP_EE	PAINPI	GDPTPI	GDEVPI	HAQPI	CRPPI	medfive
1054	80262	golimumab 50 mg	No	63.9	87.0	100.0	-99999.0	0.0	63.9
2219	80530	placebo	No	-99999.0	-99999.0	60.0	0.0	25.0	0.0
2243	80535	golimumab 50 mg	No	-99999.0	-99999.0	87.5	50.0	79.2	50.0
2273	80541	golimumab 50 mg	No	-99999.0	-99999.0	95.1	100.0	57.1	57.1
2285	80543	golimumab 100 mg	No	-99999.0	-99999.0	78.6	100.0	64.3	64.3

Obs	SJCPI	TJCPI	ACR 20W14	ACR 20	ACRNW14	acrn	ACRNEE	ACR50W14	ACR50	ACR70W14	ACR70
1054	100.0	100.0	Yes	Yes	87.0	63.9	63.9	Yes	Yes	Yes	No
2219	71.4	66.7	Yes	No	60.0	0.0	0.0	Yes	No	No	No
2243	77.8	89.5	Yes	Yes	77.8	50.0	50.0	Yes	Yes	Yes	No
2273	88.9	95.5	Yes	Yes	88.5	57.1	57.1	Yes	Yes	Yes	No
2285	85.7	84.6	Yes	Yes	82.7	64.3	64.3	Yes	Yes	Yes	No

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Appendix 7: ACR 20, ACR 50, and ACR 70 Over Time - Study C0524T08

	ACR 20			ACR 50			ACR70		
		Golimumab			Golimumab			Golimumab	
	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg	Placebo	50 mg	100 mg
Subjects Randomized	113	146	146	113	146	146	113	146	146
Using Available Data									
Week 4	5 (4%)	45 (31%)	52 (36%)	1 (1%)	14 (10%)	21 (14%)	0	1 (1%)	9 (6%)
Week 8	9 (8%)	64 (44%)	68 (47%)	1 (1%)	34 (23%)	34 (23%)	0	10 (7%)	18 (12%)
Week 14	9 (8%)	74 (51%)	66 (45%)	1 (1%)	44 (30%)	41 (28%)	1 (1%)	15 (10%)	24 (16%)
Week 16	9 (8%)	73 (50%)	74 (51%)	2 (2%)	43 (29%)	43 (29%)	1 (1%)	22 (15%)	26 (18%)
Week 20	12 (11%)	71 (49%)	80 (55%)	7 (6%)	56 (38%)	50 (34%)	1 (1%)	30 (21%)	24 (16%)
Week 24	14 (12%)	74 (51%)	89 (61%)	11 (10%)	46 (32%)	55 (38%)	4 (4%)	26 (18%)	31 (21%)
Subjects who discontinued study agent are non-responder									
Week 4	4 (4%)	44 (30%)	50 (34%)	0	14 (10%)	19 (13%)	0	1 (1%)	8 (5%)
Week 8	8 (7%)	61 (42%)	65 (45%)	1 (1%)	34 (23%)	34 (23%)	0	10 (7%)	18 (12%)
Week 14	9 (8%)	73 (50%)	64 (44%)	1 (1%)	44 (30%)	40 (27%)	1 (1%)	15 (10%)	23 (16%)
Week 16	9 (8%)	72 (49%)	74 (51%)	2 (2%)	42 (29%)	43 (29%)	1 (1%)	22 (15%)	26 (18%)
Week 20	12 (11%)	71 (49%)	76 (52%)	5 (4%)	54 (37%)	50 (34%)	1 (1%)	30 (21%)	24 (16%)
Week 24	14 (12%)	74 (51%)	85 (58%)	4 (4%)	45 (31%)	53 (36%)	1 (1%)	26 (18%)	30 (21%)

*Source: Clinical Study Report, Attachment 3.9, page 397

Appendix 8: Summary of Percent Improvement from Baseline in each of the ACR Components at Week 14 – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Number of swollen joints				
n	104	142	145	287
Mean ± SD	2.74 ± 59.973	44.66 ± 54.508	43.39 ± 57.559	44.02 ± 55.976
Median	7.50	59.90	62.50	61.50
IQ range	(-22.20, 44.55)	(10.80, 90.20)	(7.10, 88.90)	(8.30, 90.00)
Range	(-216.7, 100.0)	(-212.5, 100.0)	(-250.0, 100.0)	(-250.0, 100.0)
p-value		< 0.001	< 0.001	< 0.001
Number of tender joints				
n	104	142	145	287
Mean ± SD	-7.74 ± 70.258	42.68 ± 51.683	37.87 ± 50.769	40.25 ± 51.190
Median	0.00	53.50	43.30	46.80
IQ range	(-27.30, 38.00)	(3.40, 86.50)	(6.40, 80.00)	(5.80, 83.30)
Range	(-440.0, 100.0)	(-166.7, 100.0)	(-147.8, 100.0)	(-166.7, 100.0)
p-value		< 0.001	< 0.001	< 0.001
Patient's assessment of pain (VAS, 0-10 cm)				
n	102	139	140	279
Mean ± SD	-9.23 ± 63.306	41.11 ± 42.875	37.79 ± 46.457	39.44 ± 44.659
Median	-0.60	47.50	45.30	46.10
IQ range	(-39.00, 30.30)	(10.90, 76.90)	(8.50, 78.45)	(10.70, 76.90)
Range	(-270.6, 100.0)	(-155.2, 100.0)	(-188.9, 100.0)	(-188.9, 100.0)
p-value		< 0.001	< 0.001	< 0.001
Patient's global assessment of disease activity (VAS, 0-10 cm)				
n	102	139	140	279
Mean ± SD	-30.66 ± 125.651	38.75 ± 53.937	26.21 ± 94.886	32.46 ± 77.365
Median	1.95	49.00	43.85	44.90
IQ range	(-36.50, 26.10)	(9.10, 74.20)	(5.65, 77.15)	(6.80, 75.00)
Range	(-733.3, 91.3)	(-305.9, 100.0)	(-800.0, 100.0)	(-800.0, 100.0)
p-value		< 0.001	< 0.001	< 0.001

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Physician's global assessment of disease activity (VAS, 0-10 cm)				
n	104	141	145	286
Mean ± SD	8.25 ± 38.814	50.48 ± 42.598	50.32 ± 40.953	50.40 ± 41.698
Median	7.40	59.40	58.50	59.05
IQ range	(-12.90, 35.50)	(28.60, 82.80)	(28.00, 78.60)	(28.00, 82.50)
Range	(-129.2, 98.0)	(-96.6, 100.0)	(-147.6, 100.0)	(-147.6, 100.0)
p-value		< 0.001	< 0.001	< 0.001
HAQ score (0-3)				
n	105	140	141	281
Mean ± SD	-7.97 ± 80.391	27.19 ± 63.973	31.23 ± 95.349	29.21 ± 81.126
Median	0.00	27.95	33.30	30.80
IQ range	(-20.00, 28.60)	(0.00, 68.35)	(0.00, 87.50)	(0.00, 83.30)
Range	(-450.0, 100.0)	(-300.0, 100.0)	(-900.0, 100.0)	(-900.0, 100.0)
p-value		< 0.001	< 0.001	< 0.001
CRP (mg/dL)				
n	103	140	142	282
Mean ± SD	-24.18 ± 140.565	35.66 ± 40.508	37.21 ± 45.170	36.44 ± 42.849
Median	0.00	40.00	40.00	40.00
IQ range	(-11.10, 34.80)	(0.00, 72.50)	(0.00, 75.00)	(0.00, 75.00)
Range	(-1066.7, 94.2)	(-100.0, 95.7)	(-277.8, 95.9)	(-277.8, 95.9)
p-value		< 0.001	< 0.001	< 0.001

RE247:[E_ACR_25_A], 11JUN2007 19:18

Source: Clinical Study Report, Attachment 3.13, pages 402 – 403

Re-Analysis due to slight discrepancy in the Placebo Group

		Golimumab	
	Placebo	50 mg	100 mg
Subject's Assessment of Global Disease Activity			
n	102	139	140
Mean ± SD	-44.3 ± 185	-38.7 ± 53.9	26.2 ± 94.9
Median	2.0	49.0	43.9
IQ Range	-36.8, 26.1	9.1,74.2	5.7, 77.2
Range	-1400, 91.3	-305.9, 100	-800, 100

Appendix 9: Summary of Percent Improvement from Baseline in each of the ACR Components at Week 24 – Study C0524T08

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	113	146	146	292
Number of swollen joints				
n	105	139	145	284
Mean ± SD	-6.32 ± 79.136	45.50 ± 63.206	58.37 ± 45.518	52.07 ± 55.171
Median	0.00	67.40	71.40	69.60
IQ range	(-37.50, 52.60)	(6.30, 93.30)	(37.80, 100.00)	(27.10, 98.00)
Range	(-300.0, 100.0)	(-337.5, 100.0)	(-216.7, 100.0)	(-337.5, 100.0)
p-value		< 0.001	< 0.001	< 0.001
Number of tender joints				
n	105	139	145	284
Mean ± SD	-12.10 ± 70.449	44.72 ± 54.945	54.39 ± 45.566	49.66 ± 50.519
Median	-5.60	65.90	66.10	66.00
IQ range	(-33.30, 33.30)	(0.00, 90.90)	(32.00, 90.00)	(15.50, 90.00)
Range	(-360.0, 87.5)	(-166.7, 100.0)	(-187.0, 100.0)	(-187.0, 100.0)
p-value		< 0.001	< 0.001	< 0.001
Patient's assessment of pain (VAS, 0-10 cm)				
n	100	138	142	280
Mean ± SD	-16.04 ± 104.481	36.77 ± 82.956	42.49 ± 53.495	39.67 ± 69.524
Median	-2.25	50.00	58.15	57.00
IQ range	(-29.90, 27.55)	(8.70, 81.50)	(11.90, 82.30)	(11.25, 81.70)
Range	(-857.1, 85.1)	(-766.7, 100.0)	(-215.8, 100.0)	(-766.7, 100.0)
p-value		< 0.001	< 0.001	< 0.001
Patient's global assessment of disease activity (VAS, 0-10 cm)				
n	100	138	142	280
Mean ± SD	-22.08 ± 122.673	33.73 ± 76.230	33.42 ± 100.540	33.58 ± 89.230
Median	-1.55	52.05	52.60	52.50
IQ range	(-42.00, 27.75)	(11.40, 82.00)	(2.00, 79.40)	(7.95, 79.85)
Range	(-1100.0, 83.9)	(-500.0, 100.0)	(-1014.3, 100.0)	(-1014.3, 100.0)
p-value		< 0.001	< 0.001	< 0.001

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Physician's global assessment of disease activity (VAS, 0-10 cm)				
n	105	140	145	285
Mean ± SD	12.12 ± 43.793	57.14 ± 40.644	63.57 ± 34.235	60.41 ± 37.592
Median	4.90	70.80	66.70	68.10
IQ range	(-15.40, 45.70)	(26.80, 92.00)	(50.90, 90.60)	(43.10, 90.90)
Range	(-141.7, 96.7)	(-81.0, 100.0)	(-138.1, 100.0)	(-138.1, 100.0)
p-value		< 0.001	< 0.001	< 0.001
HAQ score (0-3)				
n	104	139	143	282
Mean ± SD	-16.07 ± 93.733	23.31 ± 99.174	35.71 ± 78.902	29.60 ± 89.525
Median	0.00	33.30	37.50	33.30
IQ range	(-25.00, 22.50)	(0.00, 84.20)	(0.00, 90.00)	(0.00, 86.70)
Range	(-450.0, 100.0)	(-800.0, 100.0)	(-700.0, 100.0)	(-800.0, 100.0)
p-value		< 0.001	< 0.001	< 0.001
CRP (mg/dL)				
n	101	136	140	276
Mean ± SD	-32.53 ± 163.975	26.07 ± 69.807	37.36 ± 42.442	31.79 ± 57.746
Median	0.00	29.15	44.05	40.00
IQ range	(-33.30, 28.60)	(0.00, 69.40)	(0.00, 73.90)	(0.00, 71.40)
Range	(-1300.0, 95.4)	(-566.7, 95.7)	(-133.3, 96.7)	(-566.7, 96.7)
p-value		< 0.001	< 0.001	< 0.001

RE247:[E_ACR_25_3], 11JUN2007 19:18

Source: Clinical Study Report, Attachment 3.14, pages 404 – 405

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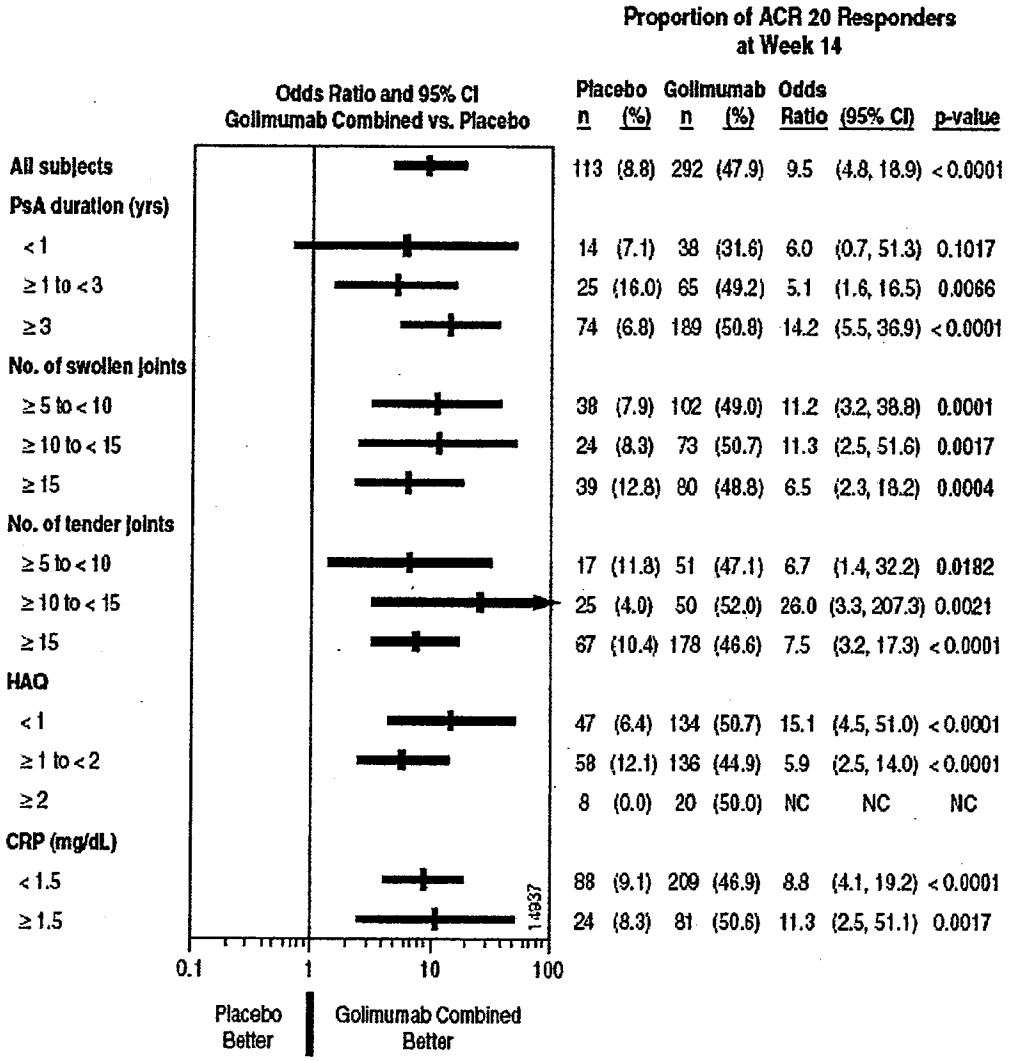
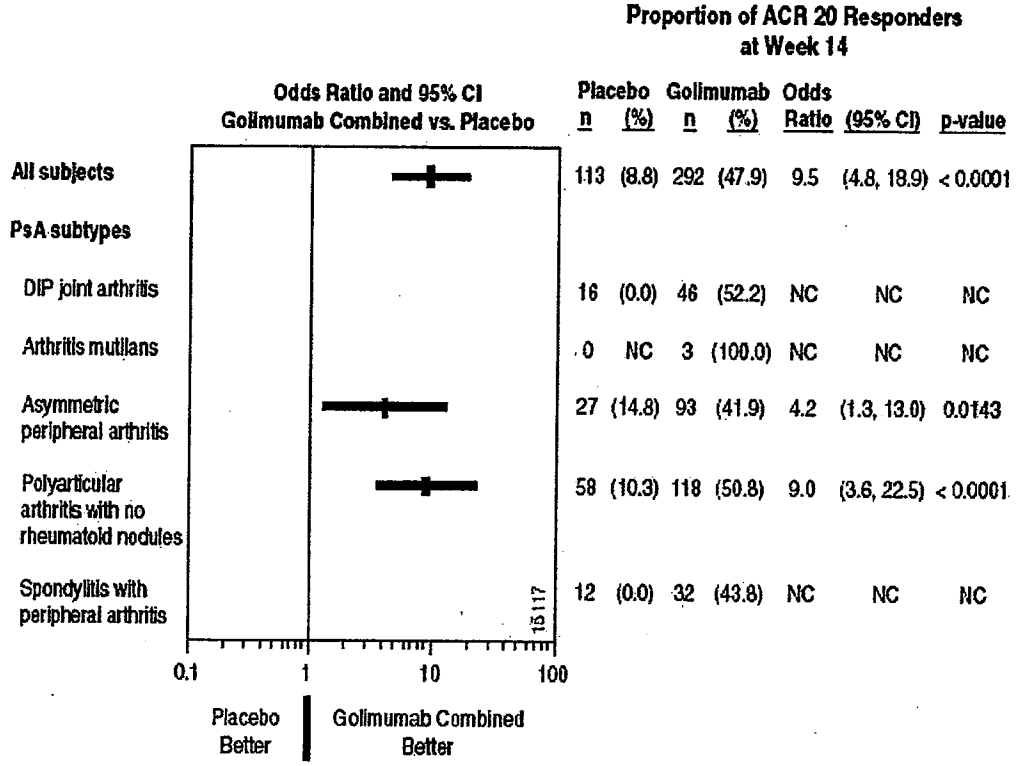
Appendix 10: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the golimumab combined group versus the placebo group for subgroups defined by baseline disease characteristics; randomized subjects



Source: Clinical Study Report, Attachment 3.71 page 482

Appendix 11: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the golimumab combined group versus the placebo group for subgroups defined by PsA baseline subtypes; randomized subjects



Source: Clinical Study Report, Attachment 3.72 page 483

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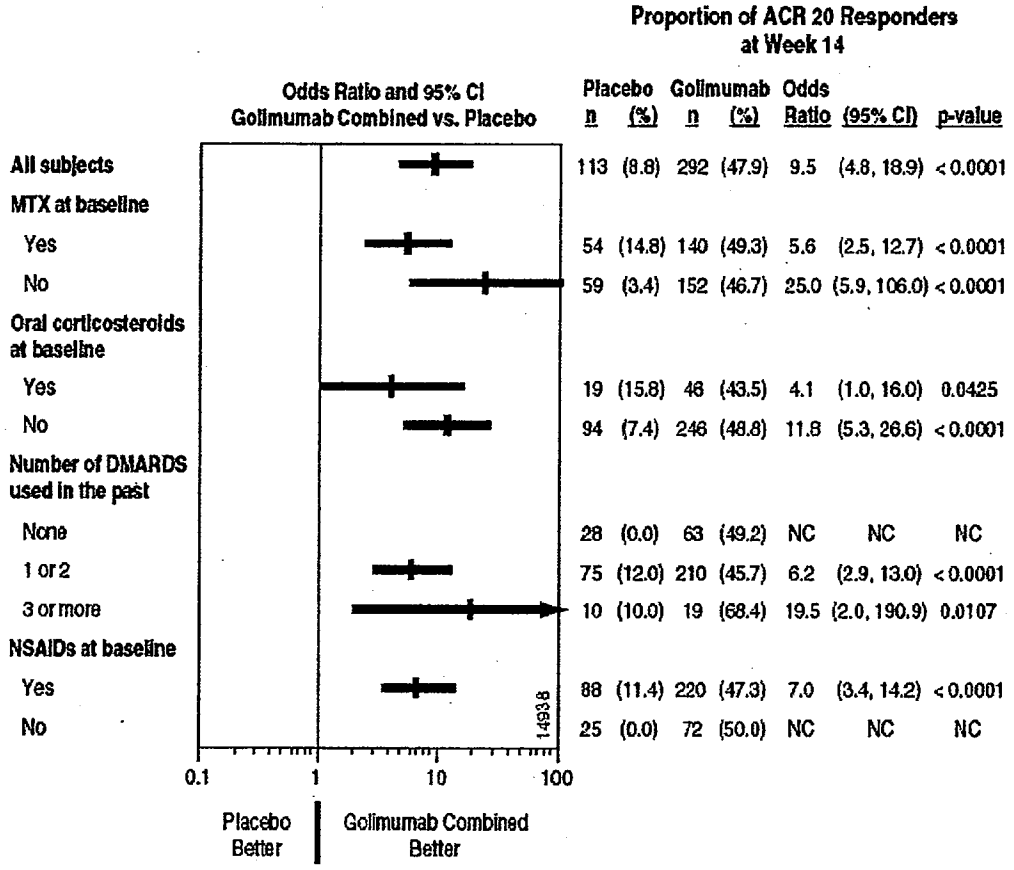
Appendix 12: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the golimumab combined group versus the placebo group for subgroups defined by baseline prior therapies for PsA; randomized subjects



Source: Clinical Study Report, Attachment 3.72 page 483

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Appendix 13: Summary of Demographics at Baseline – Randomized Subjects (Study C0524T09)

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined	Total
Subjects randomized	78	138	140	278	356
Sex					
n	78	138	140	278	356
Male	55 (70.5%)	102 (73.9%)	98 (70.0%)	200 (71.9%)	255 (71.6%)
Female	23 (29.5%)	36 (26.1%)	42 (30.0%)	78 (28.1%)	101 (28.4%)
Race					
n	78	138	140	278	356
Caucasian	57 (73.1%)	103 (74.6%)	102 (72.9%)	205 (73.7%)	262 (73.6%)
Black	1 (1.3%)	0 (0.0%)	2 (1.4%)	2 (0.7%)	3 (0.8%)
Asian	18 (23.1%)	32 (23.2%)	35 (25.0%)	67 (24.1%)	85 (23.9%)
Other	2 (2.6%)	3 (2.2%)	1 (0.7%)	4 (1.4%)	6 (1.7%)
Age (yrs)					
n	78	138	140	278	356
Mean ± SD	40.6 ± 12.71	39.2 ± 12.46	38.6 ± 11.30	38.9 ± 11.87	39.3 ± 12.06
Median	41.0	38.0	38.0	38.0	38.5
IQ range	(31.0, 50.0)	(30.0, 47.0)	(29.0, 46.0)	(29.0, 46.0)	(29.5, 47.0)
Range	(19, 69)	(18, 83)	(18, 67)	(18, 83)	(18, 83)
Weight (kg)					
n	78	138	140	278	356
Mean ± SD	77.56 ± 18.823	75.33 ± 17.733	79.76 ± 18.700	77.56 ± 18.328	77.56 ± 18.411
Median	75.00	72.65	77.50	75.15	75.15
IQ range	(64.70, 86.00)	(62.00, 85.00)	(66.00, 92.55)	(64.00, 87.80)	(64.00, 87.00)
Range	(42.0, 142.6)	(35.0, 135.0)	(47.0, 142.4)	(35.0, 142.4)	(35.0, 142.6)
Height (cm)					
n	78	138	140	278	356
Mean ± SD	170.8 ± 9.69	171.2 ± 8.58	171.0 ± 10.05	171.1 ± 9.33	171.0 ± 9.40
Median	170.0	172.0	170.0	171.0	170.8
IQ range	(164.3, 176.3)	(165.1, 178.0)	(163.9, 178.0)	(165.0, 178.0)	(164.9, 178.0)
Range	(152, 193)	(150, 196)	(148, 194)	(148, 196)	(148, 196)

Source: Clinical Study Report, Table 9, page 77 – 78

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Appendix 14: Summary of Baseline Clinical Disease Characteristics – Randomized Subjects (Study C0524T09)

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Subjects randomized	78	138	140	278
Years since inflammatory back pain first occurred				
n	78	138	140	278
Mean ± SD	16.1 ± 11.47	13.6 ± 10.37	13.2 ± 10.42	13.4 ± 10.38
Median	16.0	11.0	11.0	11.0
IQ range	(6.0, 24.0)	(6.0, 19.0)	(5.0, 18.5)	(6.0, 19.0)
Range	(0, 45)	(0, 44)	(0, 52)	(0, 52)
Years since symptoms of spondyloarthropathy first occurred				
n	78	138	140	278
Mean ± SD	16.3 ± 11.77	13.4 ± 10.43	12.3 ± 10.42	12.8 ± 10.42
Median	16.0	11.0	9.5	11.0
IQ range	(5.0, 25.0)	(6.0, 18.0)	(4.0, 18.0)	(5.0, 18.0)
Range	(0, 45)	(0, 49)	(0, 52)	(0, 52)
Duration of AS (yrs)				
n	78	138	140	278
Mean ± SD	10.81 ± 10.022	7.89 ± 8.056	8.05 ± 8.258	7.97 ± 8.144
Median	7.25	5.15	5.20	5.20
IQ range	(2.80, 18.60)	(1.60, 11.60)	(1.50, 13.25)	(1.50, 12.30)
Range	(0.1, 39.8)	(0.2, 37.8)	(0.2, 39.4)	(0.2, 39.4)
HLA-B27				
n	78	137	140	277
Positive	66 (84.6%)	112 (81.8%)	118 (84.3%)	230 (83.0%)
Negative	12 (15.4%)	25 (18.2%)	22 (15.7%)	47 (17.0%)
Prior joint surgery/procedure				
n	20	34	32	66
Subjects with any joint surgery/procedure	20 (100.0%)	34 (100.0%)	32 (100.0%)	66 (100.0%)
Synovectomy	0 (0.0%)	2 (5.9%)	0 (0.0%)	2 (3.0%)
Arthrodesis	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Joint replacement	2 (10.0%)	3 (8.8%)	2 (6.3%)	5 (7.6%)
Amputation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arthrocentesis	3 (15.0%)	1 (2.9%)	1 (3.1%)	2 (3.0%)
Steroid injection	14 (70.0%)	26 (76.5%)	24 (75.0%)	50 (75.8%)
Excision/resection	0 (0.0%)	1 (2.9%)	3 (9.4%)	4 (6.1%)
Arthrotomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arthroscopy, diagnostic	1 (5.0%)	1 (2.9%)	1 (3.1%)	2 (3.0%)
Arthroscopy, surgical	1 (5.0%)	5 (14.7%)	3 (9.4%)	8 (12.1%)
Bunionectomy	1 (5.0%)	1 (2.9%)	0 (0.0%)	1 (1.5%)
Chondroplasty	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Synovial cyst aspiration	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.5%)
Needle biopsy, synovium	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ostaotomy	1 (5.0%)	1 (2.9%)	3 (9.4%)	4 (6.1%)
Radio synovectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tendon surgery	1 (5.0%)	1 (2.9%)	0 (0.0%)	1 (1.5%)
Bursal surgery	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.5%)
Fracture reduction	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.5%)
Spine surgery	1 (5.0%)	0 (0.0%)	2 (6.3%)	2 (3.0%)

Source: Clinical Study Report, Table 10, page 79 – 80

Appendix 15: Baseline Disease Characteristics - Study C0524T09

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Golimumab Combined
Subjects randomized	78	138	140	278
Screening CRP (mg/dL)				
n	78	137	139	276
≤ 1.5	53 (67.9%)	88 (64.2%)	91 (65.5%)	179 (64.9%)
> 1.5	25 (32.1%)	49 (35.8%)	48 (34.5%)	97 (35.1%)
CRP (mg/dL)				
n	78	138	140	278
Mean ± SD	1.89 ± 2.275	1.80 ± 1.797	1.81 ± 2.107	1.81 ± 1.956
Median	1.15	1.10	0.90	1.00
IQ range	(0.30, 2.40)	(0.50, 2.50)	(0.40, 2.50)	(0.40, 2.50)
Range	(0.3, 12.0)	(0.3, 8.6)	(0.3, 10.3)	(0.3, 10.3)
Patient global assessment of disease activity VAS (0-10 cm)				
n	78	137	140	277
Mean ± SD	7.174 ± 1.6877	6.805 ± 1.7682	7.032 ± 1.8776	6.920 ± 1.8245
Median	7.200	7.000	7.200	7.100
IQ range	(6.200, 8.400)	(5.900, 8.000)	(6.000, 8.550)	(6.000, 8.200)
Range	(2.30, 9.80)	(1.50, 10.00)	(0.00, 10.00)	(0.00, 10.00)
Patient's assessment of total back pain VAS (0-10 cm)				
n	78	137	140	277
Mean ± SD	7.540 ± 1.5663	7.131 ± 1.4681	7.591 ± 1.5840	7.364 ± 1.5423
Median	7.600	7.500	7.900	7.600
IQ range	(6.600, 8.800)	(6.700, 8.200)	(6.500, 8.800)	(6.100, 8.500)
Range	(4.00, 10.00)	(4.00, 9.90)	(2.00, 10.00)	(2.00, 10.00)
Inflammation (overall morning stiffness VAS, 0-10 cm)				
n	78	138	140	278
Mean ± SD	6.804 ± 1.9914	6.718 ± 1.8624	7.374 ± 1.9258	7.049 ± 1.9195
Median	7.050	7.050	7.600	7.300
IQ range	(5.450, 8.250)	(5.400, 8.050)	(6.075, 9.000)	(5.650, 8.500)
Range	(0.15, 9.95)	(0.75, 10.00)	(0.40, 10.00)	(0.40, 10.00)
Duration of morning stiffness (minutes)				
n	78	138	140	278
Mean ± SD	75.51 ± 31.199	75.67 ± 30.734	86.10 ± 31.336	80.92 ± 31.420
Median	77.40	77.40	90.00	90.00
IQ range	(45.60, 104.40)	(52.80, 99.60)	(60.00, 117.60)	(60.00, 112.80)
Range	(1.2, 120.0)	(9.6, 120.0)	(3.6, 120.0)	(3.6, 120.0)
Chest expansion (cm)				
n	78	137	140	277
Mean ± SD	3.73 ± 1.939	4.15 ± 2.069	3.68 ± 2.044	3.92 ± 2.066
Median	3.50	3.50	3.00	3.50
IQ range	(2.30, 4.50)	(2.50, 5.50)	(2.00, 5.00)	(2.50, 5.20)
Range	(1.0, 9.5)	(0.3, 9.0)	(0.5, 9.5)	(0.3, 9.5)
Night back pain VAS (0-10 cm)				
n	78	137	140	277
Mean ± SD	6.88 ± 2.314	6.52 ± 2.234	7.23 ± 2.094	6.88 ± 2.190
Median	7.40	7.10	7.60	7.40
IQ range	(6.00, 8.60)	(5.20, 8.10)	(6.45, 8.80)	(5.70, 8.50)
Range	(0.3, 9.9)	(0.0, 10.0)	(0.0, 10.0)	(0.0, 10.0)

Source: Clinical Study Report, Table 11, page 81-82

Appendix 16: Baseline Clinical Indices – Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
BASDAI (0-10)				
n	78	138	140	278
Mean ± SD	6.608 ± 1.5221	6.498 ± 1.5687	6.893 ± 1.5006	6.697 ± 1.5447
Median	6.580	6.585	6.950	6.845
IQ range	(5.690, 7.730)	(5.600, 7.560)	(6.010, 7.850)	(5.740, 7.680)
Range	(2.39, 9.75)	(1.79, 9.58)	(3.41, 10.00)	(1.79, 10.00)
BASFI (0-10)				
n	76	138	140	278
Mean ± SD	5.098 ± 2.2512	5.001 ± 2.3758	5.168 ± 2.5593	5.085 ± 2.4669
Median	4.930	4.995	5.380	5.245
IQ range	(3.460, 6.760)	(3.210, 6.730)	(3.360, 7.290)	(3.220, 6.870)
Range	(0.89, 9.53)	(0.00, 9.56)	(0.00, 9.95)	(0.00, 9.95)
BASMI (0-10)				
n	78	137	140	277
Mean ± SD	3.86 ± 2.042	3.29 ± 2.218	3.57 ± 2.183	3.43 ± 2.201
Median	4.00	3.00	3.00	3.00
IQ range	(2.00, 5.00)	(2.00, 4.00)	(2.00, 5.00)	(2.00, 5.00)
Range	(0.0, 9.0)	(0.0, 9.0)	(0.0, 9.0)	(0.0, 9.0)
Enthesitis, Berlin index (0-12)				
n	78	137	140	277
Mean ± SD	2.24 ± 2.508	2.24 ± 2.745	2.66 ± 2.899	2.45 ± 2.827
Median	2.00	1.00	2.00	2.00
IQ range	(0.00, 3.00)	(0.00, 3.00)	(0.00, 4.00)	(0.00, 4.00)
Range	(0.0, 11.0)	(0.0, 12.0)	(0.0, 12.0)	(0.0, 12.0)
Enthesitis, UCSF index (0-17)				
n	78	137	140	277
Mean ± SD	3.63 ± 3.361	3.70 ± 3.711	4.64 ± 4.031	4.17 ± 3.898
Median	3.00	3.00	3.20	3.00
IQ range	(1.00, 6.00)	(1.00, 6.00)	(1.50, 7.00)	(1.00, 6.00)
Range	(0.0, 17.0)	(0.0, 17.0)	(0.0, 17.0)	(0.0, 17.0)
Enthesitis, MASES index (0-13)				
n	78	137	140	277
Mean ± SD	2.69 ± 3.025	2.83 ± 3.201	3.84 ± 3.358	3.34 ± 3.313
Median	2.00	2.00	3.00	2.00
IQ range	(0.00, 5.00)	(0.00, 4.00)	(1.00, 6.00)	(1.00, 5.00)
Range	(0.0, 13.0)	(0.0, 13.0)	(0.0, 13.0)	(0.0, 13.0)
Jenkins Sleep Evaluation Questionnaire (0-20)				
n	77	136	139	275
Mean ± SD	9.9 ± 4.67	10.3 ± 4.36	11.1 ± 4.79	10.7 ± 4.59
Median	9.0	10.0	11.0	11.0
IQ range	(6.0, 14.0)	(7.0, 14.0)	(8.0, 15.0)	(8.0, 14.0)
Range	(1, 20)	(0, 20)	(0, 20)	(0, 20)

Source: Clinical Study Report, Table 12, pages 83-84

Appendix 17: Discrepancies in Study C0524T09

A minor discrepancy was observed on the Applicant's efficacy datasets (subjef.xpt and visas.xpt).

> The file 'subjef.xpt' contains subject-level efficacy dataset, while the file 'visas.xpt' contains visit-level efficacy dataset. Both datasets contained the ~~ASAS20~~ASAS 20 responder, ASAS40 responder and variables used for sensitivity analyses.

In the visas.xpt, subject ID 90334 does not have baseline data on the global and the total pain measures. This implies that the change score from baseline is also missing for these endpoints, thereby this subject was coded as 'non-responder'. In subjef.xpt, this subject was coded as 'responder'.

The following are the discrepancies found at Week 14:

Obs	SUBJID	TRTGRP	POP_EE	VISIT
2094	90334	golimumab 50 mg	No	Week 0
2095	90334	golimumab 50 mg	No	Week 4
2096	90334	golimumab 50 mg	No	Week 8
2097	90334	golimumab 50 mg	No	Week 12
2098	90334	golimumab 50 mg	No	Week 14
2099	90334	golimumab 50 mg	No	Week 16
2100	90334	golimumab 50 mg	No	Week 20
2101	90334	golimumab 50 mg	No	Week 24

Obs	BSDEE	BSFEE	GDAEE	INFEE	TBPEE
2094	3.74	4.04	.	4.10	.
2095	3.23	2.92	5.6	3.05	5.4
2096	2.17	2.57	3.9	2.85	3.7
2097	3.12	3.29	4.5	2.90	4.9
2098	2.42	2.53	2.7	2.00	3.9
2099	1.62	1.92	3.3	2.10	4.7
2100	2.56	2.63	2.6	2.10	3.6
2101	2.93	2.55	3.6	2.45	3.9

Appendix 18: Summary of change from baseline in subject global assessment of disease activity score through Week 24; randomized subjects - Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
Week 4				
n	78	134	139	273
Mean ± SD	-0.73 ± 1.949	-2.45 ± 2.652	-2.25 ± 2.820	-2.35 ± 2.735
Median	-0.55	-2.05	-1.80	-2.00
IQ range	(-1.30, 0.20)	(-4.30, -0.30)	(-4.00, -0.50)	(-4.20, -0.40)
Range	(-6.2, 5.5)	(-9.4, 2.8)	(-9.7, 8.8)	(-9.7, 8.8)
Week 8				
n	77	135	137	272
Mean ± SD	-0.86 ± 2.327	-2.89 ± 2.531	-2.66 ± 3.057	-2.77 ± 2.805
Median	-1.20	-2.60	-2.30	-2.45
IQ range	(-2.20, 0.80)	(-4.80, -1.10)	(-4.90, -0.60)	(-4.85, -0.95)
Range	(-6.0, 7.0)	(-9.4, 2.6)	(-9.8, 7.4)	(-9.8, 7.4)
Week 12				
n	76	133	138	271
Mean ± SD	-0.82 ± 2.358	-2.79 ± 2.671	-2.90 ± 3.244	-2.84 ± 2.972
Median	-0.80	-2.60	-2.85	-2.70
IQ range	(-2.00, 0.65)	(-4.50, -0.90)	(-5.10, -0.70)	(-4.90, -0.90)
Range	(-6.7, 6.6)	(-9.4, 2.9)	(-9.8, 9.3)	(-9.8, 9.3)
Week 14				
n	78	132	137	269
Mean ± SD	-0.95 ± 2.467	-2.92 ± 2.828	-3.03 ± 3.143	-2.98 ± 2.987
Median	-0.80	-2.80	-3.40	-3.00
IQ range	(-2.30, 0.30)	(-5.00, -1.00)	(-5.30, -0.60)	(-5.20, -0.80)
Range	(-6.8, 7.3)	(-9.4, 4.7)	(-9.8, 9.5)	(-9.8, 9.5)
p-value		< 0.001	< 0.001	< 0.001
Week 16				
n	77	131	138	269
Mean ± SD	-0.95 ± 2.804	-3.02 ± 2.756	-2.89 ± 3.284	-2.95 ± 3.034
Median	-0.50	-2.80	-3.20	-3.00
IQ range	(-2.60, 0.60)	(-5.00, -1.00)	(-5.20, -0.70)	(-5.10, -0.80)
Range	(-8.0, 7.1)	(-9.4, 2.7)	(-9.7, 10.0)	(-9.7, 10.0)
Week 20				
n	77	126	137	263
Mean ± SD	-0.43 ± 2.460	-3.02 ± 2.803	-2.94 ± 3.255	-2.98 ± 3.042
Median	-0.10	-2.90	-3.00	-3.00
IQ range	(-1.50, 0.70)	(-5.20, -1.00)	(-5.40, -0.50)	(-5.20, -0.70)
Range	(-6.3, 7.1)	(-9.4, 3.1)	(-9.9, 8.3)	(-9.9, 8.3)
Week 24				
n	75	129	138	267
Mean ± SD	-0.64 ± 2.634	-3.09 ± 2.828	-3.30 ± 3.293	-3.20 ± 3.073
Median	-0.20	-2.60	-3.55	-3.30
IQ range	(-2.20, 1.00)	(-5.20, -1.00)	(-5.90, -0.60)	(-5.60, -1.00)
Range	(-7.1, 7.1)	(-9.4, 2.7)	(-9.9, 8.9)	(-9.9, 8.9)
p-value		< 0.001	< 0.001	< 0.001

Source: Clinical Study Report, Table 25 pages 114

Appendix 19: Summary of change from baseline in subject's assessment of total back pain through Week 24; randomized subjects - Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
Week 4				
n	78	134	139	273
Mean ± SD	-0.77 ± 2.175	-2.61 ± 2.815	-2.56 ± 2.639	-2.58 ± 2.722
Median	-0.20	-2.40	-2.20	-2.20
IQ range	(-1.60, 0.50)	(-4.80, -0.10)	(-4.00, -0.60)	(-4.40, -0.40)
Range	(-7.8, 3.9)	(-8.8, 2.9)	(-9.8, 4.5)	(-9.8, 4.5)
Week 8				
n	77	135	138	273
Mean ± SD	-0.99 ± 2.088	-3.08 ± 2.801	-3.08 ± 3.008	-3.08 ± 2.902
Median	-0.80	-2.90	-2.50	-2.90
IQ range	(-2.30, 0.10)	(-5.30, -0.60)	(-5.20, -0.80)	(-5.20, -0.70)
Range	(-7.3, 3.6)	(-8.9, 2.7)	(-9.8, 3.3)	(-9.8, 3.3)
Week 12				
n	76	133	138	271
Mean ± SD	-1.30 ± 2.577	-3.16 ± 2.903	-3.55 ± 3.061	-3.36 ± 2.985
Median	-0.50	-3.10	-3.50	-3.20
IQ range	(-2.75, 0.30)	(-5.00, -0.70)	(-5.60, -1.00)	(-5.40, -0.80)
Range	(-7.3, 3.0)	(-9.5, 2.9)	(-9.8, 2.5)	(-9.8, 2.9)
Week 14				
n	78	132	137	269
Mean ± SD	-1.45 ± 2.736	-3.17 ± 2.945	-3.47 ± 3.032	-3.32 ± 2.988
Median	-0.80	-3.50	-3.60	-3.50
IQ range	(-3.10, 0.30)	(-5.45, -0.80)	(-5.90, -0.90)	(-5.80, -0.90)
Range	(-7.4, 3.9)	(-9.5, 3.9)	(-9.8, 2.6)	(-9.8, 3.9)
p-value		< 0.001	< 0.001	< 0.001
Week 16				
n	77	131	138	269
Mean ± SD	-1.17 ± 2.836	-3.35 ± 3.007	-3.29 ± 3.170	-3.32 ± 3.086
Median	-0.50	-4.00	-3.15	-3.50
IQ range	(-2.90, 0.60)	(-5.50, -0.80)	(-5.70, -0.80)	(-5.60, -0.80)
Range	(-8.0, 4.6)	(-9.2, 4.1)	(-9.8, 4.3)	(-9.8, 4.3)
Week 20				
n	77	127	137	264
Mean ± SD	-0.91 ± 2.627	-3.23 ± 2.972	-3.42 ± 3.118	-3.33 ± 3.044
Median	-0.20	-3.20	-3.40	-3.35
IQ range	(-2.70, 0.70)	(-5.60, -0.80)	(-6.00, -0.80)	(-5.75, -0.80)
Range	(-7.6, 4.6)	(-8.8, 4.1)	(-9.8, 4.4)	(-9.8, 4.4)
Week 24				
n	75	129	138	267
Mean ± SD	-1.00 ± 2.921	-3.38 ± 3.022	-3.82 ± 3.179	-3.61 ± 3.106
Median	-0.40	-3.50	-3.90	-3.70
IQ range	(-2.00, 1.00)	(-5.60, -0.80)	(-6.40, -1.20)	(-6.30, -1.00)
Range	(-10.0, 4.6)	(-9.6, 4.1)	(-9.8, 4.4)	(-9.8, 4.4)
p-value		< 0.001	< 0.001	< 0.001

Source: Clinical Study Report, Attachment 3.17 pages 369

Appendix 20: Summary of change from baseline in inflammation (overall morning stiffness) through Week 24; randomized subjects - Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
Week 4				
n	78	134	139	273
Mean ± SD	-0.557 ± 1.9958	-2.626 ± 2.6022	-2.294 ± 2.7603	-2.457 ± 2.6841
Median	-0.175	-2.200	-1.650	-1.850
IQ range	(-1.250, 0.500)	(-4.750, -0.450)	(-4.100, -0.300)	(-4.450, -0.300)
Range	(-6.35, 4.90)	(-9.65, 2.10)	(-9.60, 7.25)	(-9.65, 7.25)
Week 8				
n	77	136	138	274
Mean ± SD	-0.947 ± 2.3393	-3.063 ± 2.6246	-3.116 ± 2.9746	-3.089 ± 2.8014
Median	-0.400	-2.825	-2.925	-2.900
IQ range	(-1.700, 0.350)	(-5.025, -1.025)	(-5.250, -0.650)	(-5.100, -0.900)
Range	(-9.00, 4.25)	(-9.40, 2.15)	(-9.80, 7.95)	(-9.80, 7.95)
Week 12				
n	76	134	138	272
Mean ± SD	-0.976 ± 2.3278	-3.151 ± 2.6918	-3.246 ± 3.0398	-3.199 ± 2.8687
Median	-0.450	-2.800	-2.950	-2.850
IQ range	(-2.250, 0.400)	(-5.300, -1.150)	(-5.450, -0.750)	(-5.375, -0.850)
Range	(-6.75, 4.90)	(-9.95, 4.05)	(-9.30, 8.10)	(-9.95, 8.10)
Week 14				
n	78	133	137	270
Mean ± SD	-1.007 ± 2.4301	-3.355 ± 2.8267	-3.374 ± 3.0109	-3.364 ± 2.9162
Median	-0.475	-3.200	-3.300	-3.250
IQ range	(-1.850, 0.700)	(-5.400, -1.150)	(-5.700, -0.800)	(-5.550, -0.950)
Range	(-7.60, 3.85)	(-9.90, 5.05)	(-9.75, 6.20)	(-9.90, 6.20)
p-value		< 0.001	< 0.001	< 0.001
Week 16				
n	77	132	138	270
Mean ± SD	-0.955 ± 2.5132	-3.374 ± 2.7471	-3.195 ± 3.2323	-3.283 ± 3.0007
Median	-0.300	-3.100	-3.100	-3.100
IQ range	(-2.250, 0.700)	(-5.425, -1.100)	(-6.000, -0.500)	(-5.450, -0.850)
Range	(-7.70, 4.05)	(-9.95, 4.10)	(-9.55, 8.30)	(-9.95, 8.30)
Week 20				
n	77	128	137	265
Mean ± SD	-0.814 ± 2.5008	-3.320 ± 2.7381	-3.324 ± 3.2419	-3.322 ± 3.0035
Median	-0.200	-3.050	-3.400	-3.250
IQ range	(-2.000, 0.700)	(-5.275, -1.250)	(-5.650, -0.950)	(-5.450, -1.100)
Range	(-8.10, 5.10)	(-9.95, 4.10)	(-9.35, 8.95)	(-9.95, 8.95)
Week 24				
n	75	130	138	268
Mean ± SD	-0.751 ± 2.3935	-3.450 ± 2.8106	-3.640 ± 3.2599	-3.548 ± 3.0461
Median	-0.200	-3.550	-3.650	-3.600
IQ range	(-2.300, 0.750)	(-5.350, -1.100)	(-6.200, -1.350)	(-5.750, -1.200)
Range	(-6.20, 4.90)	(-9.95, 4.10)	(-9.75, 8.70)	(-9.95, 8.70)
p-value		< 0.001	< 0.001	< 0.001

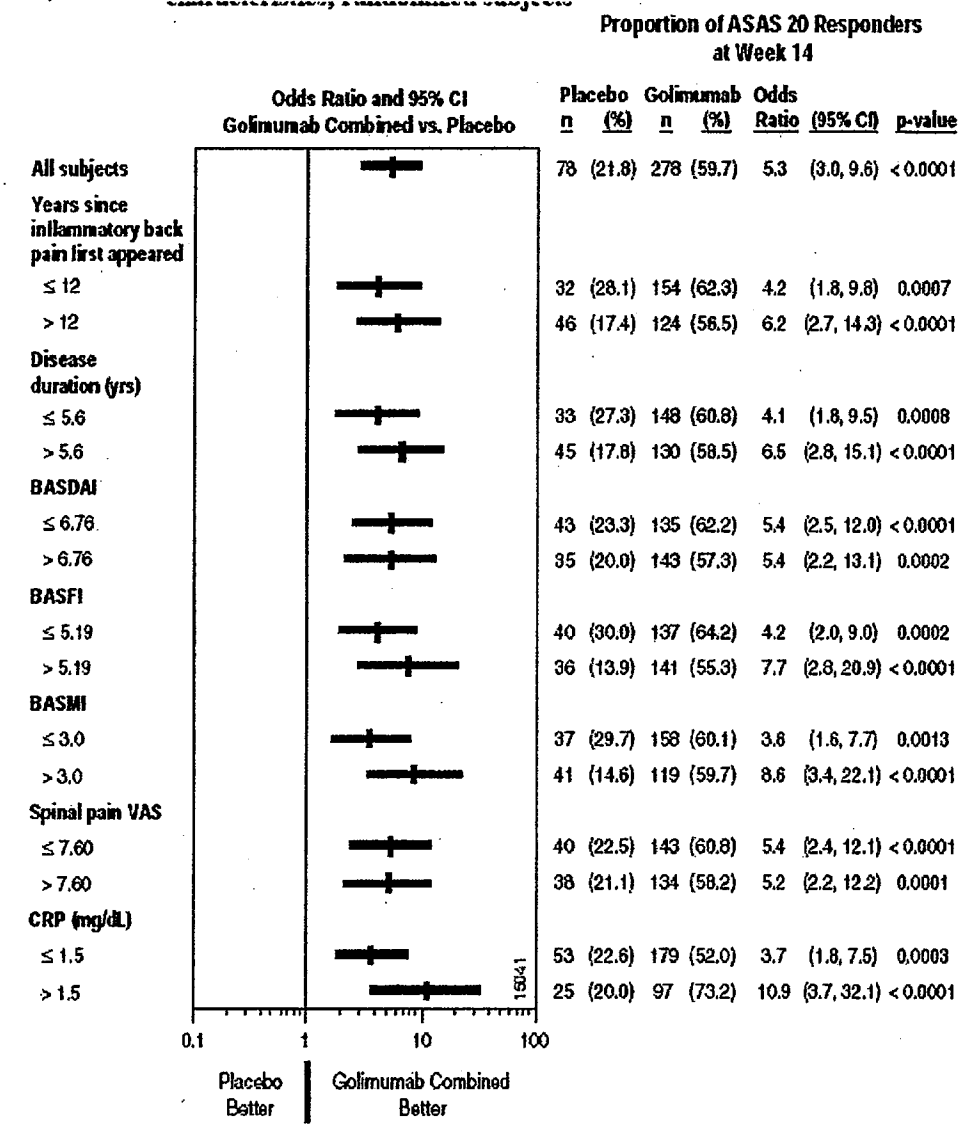
Source: Clinical Study Report, Attachment 3.20 pages 373

Appendix 21: Number of Subjects who achieved an ASAS 20 response through Week 24; randomized subjects - Study C0524T09

		Golimumab		
	Placebo	50 mg	100 mg	Combined
Subjects randomized	78	138	140	278
ASAS 20				
Week 4				
n	78	134	139	273
Subjects in response	10 (12.8%)	64 (47.8%)	63 (45.3%)	127 (46.5%)
Week 8				
n	77	135	137	272
Subjects in response	20 (26.0%)	84 (62.2%)	80 (58.4%)	164 (60.3%)
Week 12				
n	76	133	138	271
Subjects in response	20 (26.3%)	81 (60.9%)	89 (64.5%)	170 (62.7%)
Week 14				
n	78	132	137	269
Subjects in response	17 (21.8%)	83 (62.9%)	84 (61.3%)	167 (62.1%)
Week 16				
n	77	131	138	269
Subjects in response	22 (28.6%)	83 (63.4%)	81 (58.7%)	164 (61.0%)
Week 20				
n	77	126	137	263
Subjects in response	18 (23.4%)	77 (61.1%)	86 (62.8%)	163 (62.0%)
Week 24				
n	75	129	138	267
Subjects in response	18 (24.0%)	78 (60.5%)	92 (66.7%)	170 (63.7%)

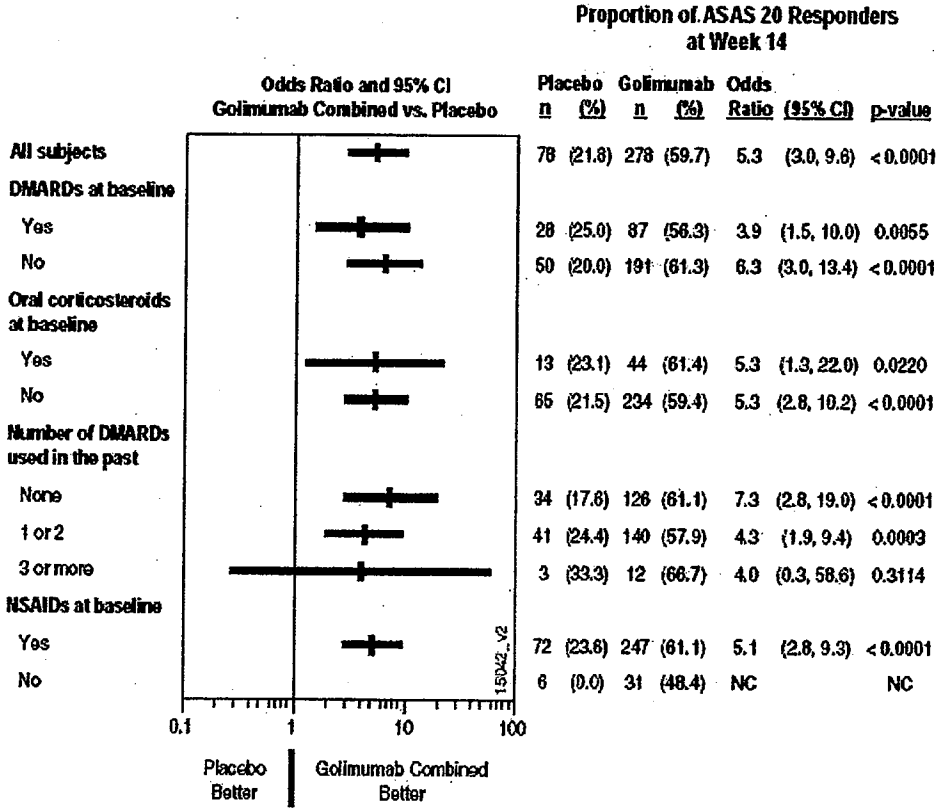
Source: Clinical Study Report, Table 22 pages 110

Appendix 22: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ASAS 20 response at Week 14 in the golimumab combined group versus the placebo group for subgroups defined by baseline disease characteristics; randomized subjects



Source: Clinical Study Report, Attachment 3.59 page 420

Appendix 23: Odds ratio (vertical bars) and 95 % confidence interval (horizontal bars) for comparing proportion of subjects who achieved ASAS 20 response at Week 14 in the golimumab combined group versus the placebo group for subgroups defined by baseline prior therapies for AS; randomized subjects



	Proportion of ASAS 20 Responders at Week 14						
	Placebo		Golimumab		Odds		
	n	(%)	n	(%)	Ratio	(95% CI)	p-value
All subjects	78	(21.8)	278	(59.7)	5.3	(3.0, 9.6)	< 0.0001
DMARDs at baseline							
Yes	28	(25.0)	87	(56.3)	3.9	(1.5, 10.0)	0.0055
No	50	(20.0)	191	(61.3)	6.3	(3.0, 13.4)	< 0.0001
Oral corticosteroids at baseline							
Yes	13	(23.1)	44	(61.4)	5.3	(1.3, 22.0)	0.0220
No	65	(21.5)	234	(59.4)	5.3	(2.8, 10.2)	< 0.0001
Number of DMARDs used in the past							
None	34	(17.6)	126	(61.1)	7.3	(2.8, 19.0)	< 0.0001
1 or 2	41	(24.4)	140	(57.9)	4.3	(1.9, 9.4)	0.0003
3 or more	3	(33.3)	12	(66.7)	4.0	(0.3, 58.6)	0.3114
NSAIDs at baseline							
Yes	72	(23.6)	247	(61.1)	5.1	(2.8, 9.3)	< 0.0001
No	6	(0.0)	31	(48.4)	NC		NC

Source: Clinical Study Report, Attachment 3.60 page 421

Signature:

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