CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125289

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Janssen Biotech, Inc.
Exhibit 2053
Accord v. Janssen
IPR2026-00259
Ex. 2053-001

3/11/09

CLINICAL PHARMACOLOGY REVIEW

BLA	STN 125289
Submission Date	6/24/2008
Brand Name	SIMPONI
Generic Name	Golimumab (Human IgG1κ monoclonal antibody)
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OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sponsor	Centocor
Relevant INDs	BB-IND 9,925, 12,723 and 12,729
Submission Type; Code	NME; 1S
Formulation; Strength(s); Administration Route	Sterile solution; 50 mg/mL in a single-use autoinjector or 50 mg/0.5 mL in a single-use pre-filled syringe; Subcutaneous injection.
Proposed Indications	1. Rheumatoid Arthritis (RA) in combination with methotrexate 2. Psoriatic Arthritis (PsA) alone or in combination with methotrexate 3. Ankylosing Spondylitis (AS)
Proposed Dosage Regimen	For all indications: 50 mg once a month, [redacted] b(4)

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1 Executive Summary

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Phase IV Commitment

Cytokines such as TNFα are known to down regulate the expression of cytochrome P450 enzymes (CYP) in humans leading to decreased metabolism of CYP substrates. In contrast,

cytokine antagonists such as basiliximab (anti-IL-2 receptor antibody) and tocilizumab (anti-IL-6 receptor antibody) are known to reverse the effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP regulation. Therefore, golimumab, an anti-TNF agent, may reverse the effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP regulation. Drug interaction with P450 substrate drugs caused by the modulation of P450s is anticipated upon initiation or discontinuation of golimumab treatment. The drug interactions may have clinical implication for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements or drug monitoring where a decrease of up to 50% could become clinically relevant. The drug interactions may also have clinical implication for P450 substrate drugs where decrease in effectiveness is undesirable.

To understand the potential effect of golimumab on P450 substrate drugs, the Sponsor should conduct post marketing *in vitro* and/or *in vivo* drug interaction studies. If warranted, the *in vivo* drug interaction study should be conducted in patients with elevated TNFα levels. A "cocktail" study with multiple P450 probe substrate drugs may be considered.

1.3 Summary of Clinical Pharmacology Findings

Golimumab (also known as CNTO 148 and rTNV148B) is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody expressed by a [redacted] cell line. Golimumab has a molecular b(4)
weight of approximately 150-151 kDa, of which [redacted]
Golimumab binds to human tumor necrosis factor alpha (TNFα), thereby neutralizing the biological activity of TNFα.

This is the first BLA application for golimumab in the U.S. (relevant INDs are: IND 9,925, 12,723 and 12,729). The Sponsor is seeking three indications: Rheumatoid Arthritis (RA) in combination with methotrexate, Psoriatic Arthritis (PsA) alone or in combination with methotrexate and Ankylosing Spondylitis (AS).

The clinical development program included five pivotal Phase 3 studies, 3 studies for RA, 1 study for PsA, and 1 study for AS to support the registration of golimumab for the treatment of RA, PsA, and AS based on 24-week efficacy and safety data from these studies. The safety of golimumab is further supported by clinical experience beyond 24 weeks in the 5 Phase 3 studies together with safety data from Phase 1 and 2 studies in RA patients, completed and ongoing studies in other indications, and Phase 1 studies in healthy subjects. The doses of 50 mg or 100 mg every 4 weeks for 24 weeks were studied in the Phase 3 studies. The Sponsor proposed a dose regimen of 50 mg given as a SC injection once a month, [redacted] No b(4)
clinical studies of golimumab have been conducted in pediatric populations. The Sponsor is asking deferral and partial waiver for pediatric RA and PsA patients and full waiver for AS indications.

Mechanism of Action: TNFα is considered a key inflammatory mediator that exhibits a wide variety of functional activities. Abnormally high levels of TNFα have been implicated in the pathophysiology of several immune-mediated diseases, including Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS). Binding of TNF by an anti-TNF antibody prevents the target from binding to cell surface TNF receptors, and consequently

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prevents downstream signaling cascades and deleterious effects of inappropriate or excessive TNF expression.

Product Development and Comparability among Product Lots: During the clinical development of golimumab, clinical materials from 2 cell lines ([redacted] , as well as different formulations (lyophilizaed and liquid formulations) were studied. Lyophilized formulations were used for the early Phase 1 and Phase 2 studies, and a liquid formulation supplied in a glass vial (liquid in vial [LIV]) was used in all Phase 3 studies or in a prefilled syringe (PFS) used in several healthy volunteer Phase 1 studies and in all Phase 3 (post Week 24) studies. The final product will be liquid formulation of golimumab in a PFS fitted with the [redacted] or the same PFS in an autoinjector. b(4) b(4)

A biochemical equivalency study was performed to demonstrate that product made by the two cell lines [redacted] was equivalent. A nonclinical, single SC dose PK comparison study of the material produced by the cell lines [redacted] showed that golimumab produced from the 2 different cell lines had similar PK profiles in cynomologus monkeys (Study P-2002-008). See Product and Pharm/Tox reviews for additional details. b(4)

The liquid and lyophilized formulations were found to be comparable in a nonclinical pharmacokinetic comparability study (Study P-2005-003). See Pharm/Tox review for additional details.

The comparability of the PFS with the Phase 3 LIV presentation and the PFS in the autoinjector presentations were conducted with 1) A thorough *in vitro* comparability assessment of LIV and PFS to compare product quality attributes and stability profiles and 2) A Phase 1 bioequivalence study (Study C0524T24) to assess the PK comparability of the 2 injection methods (ie, 100 mg golimumab single dose administered using an autoinjector versus a needle and syringe) for the delivery of SC golimumab in healthy subjects. The results showed the 90% confidence interval (CI) for the ratio of geometric mean AUC(0-49D) values between the 2 injection methods (autoinjector vs. LIV) was 95.17% to 120.55%, which was between the 80% and 125% range; while the 90% CI for Cmax was 96.14% to 127.42%, which fell slightly outside the upper limit of 80% to 125% range. Although the data did not show bioequivalence with Cmax, the difference is small and not considered clinically significant. The Sponsor is proposing a 50 mg dose, and a 100 mg dose was studied in clinical studies with acceptable safety profiles. Therefore, slightly higher Cmax with autoinjector would not pose a safety concern.

In vitro assessment during IND found an increased number of subvisible particles in the PFS. Therefore, a recommendation was made to require clinical data to demonstrate that differences between the presentations will not result in clinically meaningful differences in immunogenicity and safety (PreBLA meeting minutes). The comparison of safety and immunogenicity of autoinjector vs. LIV was analyzed in the on-going Phase 3 studies and the report was reviewed by the Medical Officer. Refer to clinical review for details.

Pharmacokinetics Findings:

Healthy Subjects: Three PK studies (Studies C0524T13, C0524T13, and C0524T24) were conducted in healthy subjects (single dose, 50 or 100 mg) following subcutaneous injection. Mean CL/F was 12-19 mL/day/kg, mean Vz/F was 224-262 mL/kg, and mean apparent $T_{1/2}$ was 11-13 days. Pharmacokinetics was similar between Caucasian and Japanese subjects.

RA Patients: Two PK studies (Studies C0466T01 and C0466T02) were conducted in RA patients via IV and SC route, respectively. In these studies, dose proportionality and relative bioavailability were determined. PK of golimumab was dose-proportional between doses of 0.3 to 3 mg/kg following both IV and SC dosing. Mean CL/F in RA patients following SC was 10-13 mL/day/kg, mean Vz/F was 214-737 mL/kg, and mean apparent $T_{1/2}$ was 12-24 days.

Based on a cross-study comparison of mean AUC_{inf} data at dose levels of 0.3 mg/kg and 3.0 mg/kg from studies C0466T02 (SC) and C0466T01 (IV), the absolute bioavailability of golimumab after a SC administration was estimated to be 44% and 58%, respectively. The ratio of mean dose-normalized AUC_{inf} (SC vs IV) was 53%.

Population PK Analyses: POP-PK analysis was conducted based on data obtained from 2 Phase 3 studies for RA. In addition, POP-PK analysis was conducted from each one of Phase 3 study for AS and PsA. There was not dense PK data for AS and PsA patients.

PK parameters estimated from the POP-PK models are listed in Table 1.

Table 1. Summary of Typical Population PK Parameters in the Three Disease Populations (RA, PsA, and AS).

Population PK Parameter Estimate (95% CI)[a]	RA	PsA	AS
CL/F (L/day)[b]	1.91 (1.80-2.03)	1.38 (1.30-1.47)	1.41 (1.31-1.51)
V/F (L)[b]	26.7 (24.5-28.7)	24.9 (22.7-26.9)	22.6 (20.7-24.4)
Ka (1/day)	0.668 (0.564-0.875)	0.908 (0.701-1.170)	1.010 (0.760-1.460)

[a]Typical population PK parameters estimated by NONMEM with the original final population PK dataset, and 95% confidence intervals calculated using 1,000 re-sampled and successfully converged bootstrapping runs are presented.
[b]Based on standardized weight of 70 kg

Pharmacokinetics in Special Populations: Although no specific PK studies were conducted, based on the results of the POP-PK analyses, body weight was the most significant covariate identified for both CL/F and V/F of golimumab. Age and race (mainly Caucasian vs. Asian) did not appear to impact on the PK of golimumab in adult RA, PsA, and AS patients. Population PK analysis suggested no PK difference between genders after body weight adjustment in RA and PsA patients. In AS study, gender was a significant covariate based on covariate analysis and females showed 13% higher apparent clearance than males after body weight adjustment.

No clinical studies of golimumab have been conducted in pediatric populations.

No formal PK studies were conducted in subjects with renal or hepatic impairment.

Exposure-Response:
Dose Selection: The selected doses and dosage regimens for the Phase 3 studies in RA, PsA, and AS were golimumab 50 mg and 100 mg SC every (q) 4 weeks. These doses were chosen based on the results of nonclinical studies, a Phase 2 dose-ranging study of golimumab in RA subjects (Study C0524T02), and Sponsor's clinical experience with infliximab (REMICADE®), another anti-TNFα mAb.

ER for Efficacy and Safety: The efficacy and safety of two dosage regimens of golimumab (50 mg and 100 mg SC q4 weeks) were evaluated in the 5 Phase 3 studies in subjects RA, PsA, or AS. Similar to findings in the Phase 2 dose-ranging study, overall, treatment with either golimumab 50 mg or 100 mg q4 weeks showed similar efficacy. The safety profiles were also similar between the two doses studied with 50 mg showing lower adverse event rates in some categories. 50 mg was selected as the marketing dose.

Immunogenicity: The combined antibody to golimumab incidence across all subjects treated in Phase 3 (50 and 100 mg) was 57 of 1322 subjects (4.3%), ranging from 2.1% in C0524T06 to 6.3% in C0524T05. The proportion of subjects with antibodies to golimumab through Week 24 was similar across the different indications, with no notable difference in total antibody incidence between RA, PsA, and AS.

Higher antibody rates were generally observed for subjects receiving golimumab in the absence of methotrexate (MTX) based on the available data (Studies C0524T08, C0524T09 and C0524T11). Across these 3 studies, the antibody incidence was 12 of 169 (7.1%) for subjects receiving 50 mg golimumab in the absence of MTX and was 5 of 300 (1.7%) for subjects receiving 50 mg and MTX.

Positive antibody to golimumab status (ie, positive IR status, IRP) is generally associated with lower serum golimumab concentrations across the 5 Phase 3 studies.

The small number of patients positive for antibodies to golimuma and lack of clear exposure-response in the dose/exposure range studied limit the ability to have a definitive conclusion regarding the relationship between immunogenicity and clinical efficacy and safety measures.

In the Phase 2 RA study (C0524T02), neutralizing antibodies were measured in samples from subjects classified as positive for antibodies to golimumab in the bridging EIA. Eight (47%) out of 17 evaluable subjects were positive for the presence of neutralizing antibodies to golimumab. A higher proportion of subjects with neutralizing antibodies were observed in the 50 mg groups relative to the 100 mg groups. The rate could be assay dependent, i.e., reflects differences in the sensitivity of the bridging EIA and neutralization antibody assay.

Drug-Drug Interactions: IgG antibodies are not metabolized by cytochrome P450s (CYPs). No *in vitro* metabolic-based drug-drug interaction studies using human hepatocytes or hepatic

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microsomes were conducted for golimumab. Effect of co-administered small molecular weight drugs on golimumab via the CYP inhibition or induction is not expected. No formal drug-drug interaction assessment for golimumab and other drugs or biologics was performed.

Disease modifying antirheumatic drugs (DMARDs, such as MTX), NSAIDs, and oral corticosteroids are commonly used for treatment of RA, PsA or AS and used in the Phase 3 studies. The effects of these selected concomitant medications on golimumab PK were evaluated in the covariate analysis with POP-PK data.

The presence of MTX decreased apparent CL for golimumab. Mean trough levels at steady-state in the presence of MTX were approximately 33%, 25%, 67% higher than those in the absence of MTX in AS, PsA, and RA patients, respectively. The covariate analysis showed that concomitant use of MTX was a significant covariate for apparent CL/F in RA subjects but not in PsA and AS subjects. The results showed that MTX reduced golimumab CL/F by 17.1% in the RA population PK analysis.

Smoking status was found to be a significant covariate for CL/F in the PsA population, but not in the RA and AS populations. Subjects with PsA who were smokers had an estimated 13% higher CL/F of golimumab compared with nonsmoking subjects. Because of lack of exposure-response in the dose range studied (50-100 mg), 13% change in apparent clearance is not likely to be clinically significant. Smoking is known to induce CYP1A2-mediated drug metabolism for small molecular drugs. The mechanism by which smoking may influence the disposition of monoclonal antibodies remains unclear.

No other commonly coadministered drugs including NSAIDs, corticosteroids, sulfasalazine (SSZ), or hydroxychloroquine showed to affect golimumab PK based on covariate analysis.

Golimumab, however, might indirectly influence the expression level of P450 enzymes leading to altered P450 activities in RA patients because TNFα is known to reduce the expression level of multiple P450 enzymes including CYP3A4.[1] Upon initiation or discontinuation of golimumab, the P450 levels may increase or decrease leading to altered P450 activities. Therefore, drug interaction of golimumab with P450 substrate drugs caused by the modulation of P450s is anticipated.

The drug interactions may have clinical implication for P450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements (e.g., warfarin) or drug monitoring (e.g., cyclosporine or theophylline) where a decrease of up to 50% could become clinically relevant. The drug interactions may also have clinical implication for P450 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives.

Golimumab has not been studied in combination with biological DMARDs such as other TNF antagonists.

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[1] Aitken and Morgan. Gene-Specific Effects of Inflammatory Cytokines on Cytochrome P450 2C, 2B6, and 3A4 mRNA Levels in Human Hepatocytes. *Drug Metab. Disp.* 35(9):1687-1693, 2007.

QT/QTc Evaluation: A thorough QT/QTc study was not conducted for golimumab because it is generally not required for a momoclonal antibody biological product.

Adverse Events: Treatment with golimumab was generally well tolerated in patients with RA, PsA, or AS. The types of clinically important AEs were generally similar to those reported for other anti-TNF agents.

An Optional Inter-Divisional-Level Clinical Pharmacology briefing took place on February 18, 2009.

Lei Zhang 3/9/09

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Concurrence: 3/11/09

Venkatesh Atul Bhattaram, Ph.D.

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2 Question-Based Review (QBR)

Reviewer's Notes: Golimumab, CNTO 148, and rTNV148B are used interchangeably in this review. The proposed trade name is SIMPONI.

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Golimumab (also known as CNTO 148 and rTNV148B) is a human monoclonal antibody with an immunoglobulin G (IgG)1 heavy chain isotype [redacted] light chain isotype (Figure 2.1.1.1). Golimumab binds to both soluble and transmembrane forms of tumor necrosis factor alpha (TNFα) and inhibits TNFα bioactivity. b(4)

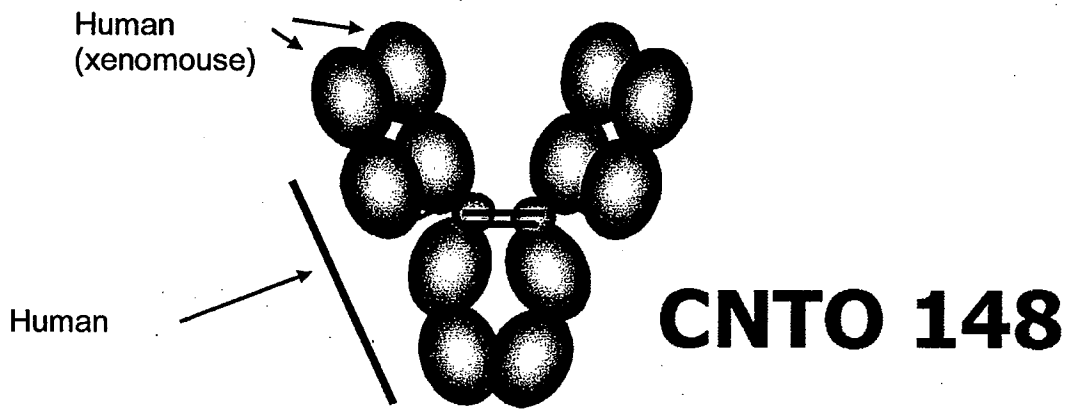

Figure 2.1.1.1. Structure Scheme of Golimumab.

Golimumab has a molecular weight of approximately 150-151 kDa, of which [redacted] b(4)

Golimumab was expressed by a [redacted] cell line. The drug substance is manufactured by [redacted] b(4)

Formulation: The golimumab PFS formulation is composed of 100 mg/mL golimumab with excipient concentrations of 5.6 mM L-histidine, 4.1% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80, pH 5.5. It is manufactured in two dosages, a 50 mg/syringe (0.5 mL) and a 100 mg/syringe (1.0 mL). The Sponsor will only market the 50 mg/syringe presentation for administration by SC injection for the proposed indications.

2.1.2 What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?

Mechanism of Action: Tumor necrosis factor (TNF) has been identified as a key sentinel cytokine that is produced in response to various stimuli and subsequently promotes the inflammatory response through activation of the caspase-dependent apoptosis pathway and the transcription factors nuclear factor (NF)- κB and activator protein-1 (AP-1). TNF also modulates the immune response through its role in the organization of immune cells in germinal centers. Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis, as well as spondyloarthropathies such as psoriatic arthritis and ankylosing spondylitis, and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF, which prevents the binding of TNF to its receptors. Currently, three other TNFα blockers have been approved for the treatment of RA, AS or PsA: infliximab, etanercept, and adalimumab (Table 2.1.2.1).

Table 2.1.2.1. Approved TNFα blockers for the same proposed indications as golimumab.

Product	Year of approval	Description	Indications	
			Adult	Pediatric
Infliximab (REMICADE)	**1998**	Monoclonal Antibody	**RA, PsA, AS**, Ps, CD, UC	CD
Etanercept (ENBREL)	**1998**	Fusion Protein	**RA, PsA, AS**, Ps	JIA
Adalimumab (HUMIRA)	**2002**	Monoclonal Antibody	**RA, PsA, AS**, Ps, CD	JIA

Ps: Psoriasis; CD: Crohn's Disease; UC: Ulcerative Colitis; JIA: Juvenile Idiopathic Arthritis

Proposed Indications (Extracted from the proposed labeling):

Rheumatoid Arthritis (RA):

SIMPONI, in combination with methotrexate, is indicated for [redacted] in adult patients with moderate to severely active rheumatoid arthritis. b(4)

Psoriatic Arthritis (PsA):

SIMPONI, alone or in combination with methotrexate, is indicated for [redacted] [redacted] active arthritis in adult patients with psoriatic arthritis. b(4)

Ankylosing Spondylitis (AS):

SIMPONI is indicated for [redacted] adult patients with active disease. b(4)

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Proposed Dosage and Route of Administration:
SIMPONI is administered by subcutaneous injection. 50 mg of SIMPONI administered once a month, [redacted] for all three indications. b(4)

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 11 studies contain human PK data for golimumab (Table 2.2.1.1):

- 3 Single-dose studies in healthy subjects (50 or 100 mg, race, BE)
- 3 Phase 1/2 studies in RA patients (dose proportionality, SC vs. IV, and dose-finding)
- 3 Phase 3 studies in RA patients (POP-PK analysis with data from 2 studies)
- 1 Phase 3 study in AS patients (POP-PK analysis)
- 1 Phase 3 study in PsA patients (POP-PK analysis)

In addition, PK studies were conducted in patients with asthma and [redacted] however, data were not be reviewed (Studies C0524T03 and C0524T01). b(4)

Table 2.2.1.1. Overview of Clinical Pharmacology Studies Relevant to the Proposed Indications.

Study	Population	Formulation	Route	Sampling Scheme	No. of Subjects
C0524T13	HV	[redacted]	SC, 100 mg SD	Intensive	30
C0524T23	HV (Japanese vs. Caucasian)	[redacted]	SC, 50 and 100 mg SD	Intensive	51
C0524T24	HV (BE, methods)	[redacted]	SC, 100 SD	Intensive	156
C0466T01	RA	[redacted]	IV, 0.1-10 mg/kg SD	Intensive	36
C0466T02	RA	[redacted]	SC, 0.3-3 mg/kg SD 0.3 and 1 mg/kg q 2w x 3	Intensive	53
C0524T02	RA	[redacted]	SC, 50 and 100 mg q2w or q 4 w	Sparse	172
C0524T05	RA	[redacted]	SC, 50 and 100 mg q 4w	Sparse	637
C0524T06	RA	[redacted]	SC, 50 and 100	Sparse	444

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			mg q 4w		
C0524T11	RA	[redacted]	SC, 50 and 100 mg q 4w	Sparse	461
C0524T08	PsA	[redacted]	SC, 50 and 100 mg q 4w	Sparse	405
C0524T09	AS	[redacted]	SC, 50 and 100 mg q 4w	Sparse	356

b(4)

SD: single dose

Three Phase 3 RA studies were conducted to evaluate 3 different subpopulations of subjects with moderate to severe active RA (Table 2.2.1.2):

- **C0524T05 (5):** subjects with active RA naïve to MTX and no prior treatment with an anti-TNF agent
- **C0524T06 (6):** subjects with active RA despite MTX treatment and no prior treatment with an anti-TNF agent
- **C0524T11(11):** subjects with active RA previously treated with 1 or more anti-TNF agents

Table 2.2.1.2. 3 Randomized, Double-Blind, Controlled, Global, 5-Year, Ongoing, Phase 3 Trials in Patients with Active RA.[1]

Study	Design	Treatment Groups	Additional Concomitant Medications
5	MTX-controlled trial in patients with **active RA** who are **MTX-naive** (i.e., have not received more than 3 weekly doses of MTX for RA at any time).	1. MTX (n=160) 2. Golimumab100 (n=159) 3. Golimumab50 & MTX (n=159) 4. Golimumab100 & MTX (n=159)	≤ 10 mg prednisone/day and/or NSAIDs
6	PC trial in patients with **active RA despite MTX therapy**.	1. Background MTX (n=133) 2. Golimumab100 (n=133) 3. Golimumab50 & background MTX (n=89) 4. Golimumab100 & background MTX (n=89)	≤ 10 mg prednisone/day and/or NSAIDs
11	PC trial in patients with **active RA who must have previously received ≥ 1 dose of a biologic TNF inhibitor** without a clinically serious adverse reaction.	1. Placebo ± DMARDS (n=155) 2. Golimumab50 ± DMARDS (n=153) 3. Golimumab100 ± DMARDS (n=153)	MTX, HCQ, SSZ, ≤ 10 mg prednisone/day, and/or NSAIDs

[1] This BLA contains 24 weeks of data from the ongoing, 5-year studies
[2] In the Phase 3 RA trials, early escape (EE) if < 20% improvement in both swollen and tender joint count. In Studies 6 & 11, EE possible at Week 16 and in Study 5 EE possible at Week 28.

Mean durations of disease in Studies 5 (MTX-naïve), 6 (MTX non-responders), and 11 (prior TNF inhibitor use) were 3.5, 8.3, and 11.8 years, respectively.

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In Studies 5, 6, and 11, 55%, 75%, and 99% of patients had prior exposure to ≥ 1 DMARD, respectively.

One Phase 3 study each was conducted in PsA (Study 8) and AS (Study 9) patients (Table 2.2.1.3).

Table 2.2.1.3. 3 Randomized, Double-Blind, Controlled, Global, 5-Year, Ongoing, Phase 3 Trials in Patients with PsA and AS.[1]

Study	Design[2]	Treatment Groups	Additional Concomitant Medications
8	Patients with **active PsA** (≥ 3 swollen joints and ≥ 3 tender joints) **despite NSAID or DMARD therapy**. Must have active plaque Ps (≥ 2 cm in diameter). Cannot receive topical or systemic Ps treatments during the study.	1. Placebo ± MTX (n=113) 2. Golimumab50 ± MTX (n=146) 3. Golimumab100 ± MTX (n=146)	MTX (≤ 25 mg/week), ≤ 10 mg prednisone/day, and/or NSAIDs
9	Patients with **active AS** (BASDAI score ≥ 4 & total back pain score ≥ 4 out of 10) who have had an **inadequate response to NSAIDs or** are **unable to tolerate NSAIDs**. Cannot have complete ankylosis of the spine	1. Placebo ± DMARDS (n=78) 2. Golimumab50 ± DMARDS (n=138) 3. Golimumab100 ± DMARDS (n=140)	MTX (≤ 25 mg per week), HCQ, SSZ, ≤ 10 mg prednisone/day, and/or NSAIDs

1 This BLA contains 24 weeks of data from the ongoing, 5-year studies
2 In Study 8, early escape (EE) at Week 16 if < 10% improvement in both tender & swollen joint counts. In Study 9, EE at Week 16 if < 20% improvement in total back pain and morning stiffness.

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2.2.2 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?

Efficacy:
RA:
Study T05:
Primary endpoint: Proportion ACR50 (American College of Rheumatology) response at Week 24

An ACR 50 response was defined as ≥ 50% improvement in 1 and 2 below (see ACR20 definition).

Study T06:
Co-primary endpoints:
1. Proportion ACR 20 at Week 14
2. Change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24

An ACR 20 response was defined as:
1. ≥ 20% improvement in swollen joint count (66 joints) and tender joint count (68 joints); and
2. ≥ 20 % improvement in 3 of the following 5 assessments:
   - Patient's assessment of pain on a 0 to 10 cm VAS scale (no pain to the worst possible pain)
   - Patient's global assessment of disease activity on a 0 to 10 cm VAS scale (very well to very poor)
   - Physician's global assessment of disease activity on a 0 to 10 cm VAS scale (no active arthritis to extremely active arthritis)
   - Patient's assessment of physical function as measured by the HAQ on a scale of 0 to 3 (without any difficulty to unable to do)
   - C-reactive protein (CRP)

Study T11:
Primary endpoint: Proportion ACR 20 at Week 14

RA Efficacy Results (provided by the medical reviewer, Dr. Brodsky):

Results from Studies 6 and 11 show strong evidence of efficacy for golimumab plus MTX: Study 5 results are marginal but supportive. Overall, in different RA populations (e.g., different disease durations, concomitant medications), golimumab & MTX at 50 mg demonstrated efficacy in signs & symptoms compared to the control group (Table 2.2.2.1). The pre-specified sign and symptom primary efficacy endpoints are highlighted in yellow.

Table 2.2.2.1. Major Sign and Symptom Efficacy Endpoints at Weeks 14 and 24 in the 3 Phase 3 RA Studies (i.e., Studies 5, 6, and 11).[1]

Study 5 (MTX naïve)		MTX (n=161)	Golimumab 100 (n=159)	Golimumab 50 & MTX (n=159)	Golimumab 100 & MTX (n=159)
ACR 20 responders		**49%**	**52%**	**62%**	**62%**
ACR 50 responders		**29%**	**33%**	**40%**	**37%**
p-value (versus MTX)		**—**	**0.521**	**0.042**	**0.177**
ACR 70 responders		**16%**	**14%**	**24%**	**18%**
ACR-N Index, mean (SD)		**20 (48)**	**21 (47)**	**28 (70)**	**27 (51)**
Study 6 (inadequate MTX response)		**MTX (n=139)**	**Golimumab 100 (n=133)**	**Golimumab 50 & MTX (n=139)**	**Golimumab 100 & MTX (n=139)**
ACR 20 responders	**Week 14**	**33%**	**44%**	**55%**	**56%**
	p-value (vs. MTX)	**—**	**0.059**	**0.001**	**< 0.001**
	Week 24	**28%**	**35%**	**60%**	**60%**
ACR 50 responders	**Week 14**	**10%**	**20%**	**35%**	**29%**

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	Week 24	14%	20%	37%	33%
ACR 70 responders	Week 14	4%	8%	13%	9%
	Week 24	5%	11%	20%	15%
ACR-N Index, mean (SD)	Week 14	-10 (62)	-4 (78)	23 (46)	19 (51)
	Week 24	-17 (84)	-8 (83)	22 (58)	28 (38)
Study 11 (prior use TNF inhibitor)		Placebo + DMARDs (n=155)	—	Golimumab50 + DMARDs (n=153)	Golimumab100 + DMARDs (n=153)
ACR 20 responders	Week 14	18%	—	35%	38%
	p-value (vs. MTX)	—	—	< 0.001	< 0.001
	Week 24	17%	—	34%	44%
ACR 50 responders	Week 14	6%	—	16%	20%
	Week 24	5%	—	18%	20%
ACR 70 responders	Week 14	2%	—	10%	9%
	Week 24	3%	—	12%	10%
ACR-N Index, mean (SD)	Week 14	-17 (64)	—	10 (49)	6 (55)
	Week 24	-33 (96)	—	7 (50)	16 (44)

Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks. For Study 5, MTX is 20 mg of oral MTX given once weekly (starting dose of MTX 10 mg and then escalation to 20 mg by Week 20). For Study 6, MTX is the background weekly oral MTX used prior to enrollment (15-25 mg). For Studies 5, 6, and 11 patients may have taken stable doses of concomitant NSAIDs and/or corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. For Study 11, patients may have also taken stable doses of concomitant MTX, sulfasalazine, and/or hydroxychloroquine during the study.
1 The pre-specified statistical population for all ACR responder efficacy analyses in Studies 5, 6, and 11 were all randomized patients. The primary efficacy endpoint in Study 5 was the proportion of patients that achieved an ACR 50 response at Week 24 and the primary efficacy endpoint in Studies 6 and 11 were the proportion of patients that achieved an ACR 20 response at Week 14. The pre-specified sign and symptom primary efficacy endpoints are highlighted in yellow.

PsA:
Study T08:
Two co-primary endpoints:

- The proportion of subjects achieving an ACR 20 response at Week 14 (this BLA)
- The change from baseline in total radiographic scores of the hands and feet at Week 24 b(4)

ACR 20 response, originally designed to evaluate efficacy in RA subjects, was chosen as the measure for the primary endpoint based on the clinical similarity of PsA and RA and the wide acceptance of ACR 20 by rheumatologists and regulatory authorities as a measure of improvement in the signs and symptoms of the arthritic component of PsA.

PsA Efficacy Results (provided by Dr. Brodsky):

Golimumab 50 mg and golimumab 100 mg are effective in reducing signs and symptoms of PsA. Large treatment effects of golimumab were observed compared to placebo (Table 2.2.2.2). The proportion of ACR 20 responders was generally similar regardless of MTX use at baseline. The pre-specified sign and symptom primary efficacy endpoints are highlighted in yellow.

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Table 2.2.2.2: Major Sign and Symptom Efficacy Endpoints at Weeks 14 and 24 in Study 8

		Placebo + MTX	Golimumab50 + MTX	Golimumab100 + MTX
Randomized patients[1]		113	146	146
ACR 20 responders[2]	Week 14	9%	51%	45%
	p-value vs. placebo	—	< 0.001	< 0.001
	Week 24[3]	12%	52%	61%
ACR 50 responders	Week 14	2%	30%	28%
	Week 24[4]	4%	32%	38%
ACR 70 responders	Week 14	1%	12%	17%
	Week 24[4]	1%	19%	21%
ACR-N Index, mean (SD)	Week 14	-36 (67)	16 (53)	15 (55)
	Week 24	-38 (71)	14 (62)	31 (49)
Patients with W24 DAS28 (CRP)		97	134	137
DAS28 (CRP)[5], mean	Baseline	4.4	4.4	4.3
	Week 24	4.3	3.0	2.7
	Change	0.1	1.4	1.6

Patients may have taken stable doses of concomitant MTX, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks

[1] Randomized patients was the primary statistical population for the efficacy analyses in Study 8.

[2] ACR 20 responders at Week 14 was the first co-primary efficacy endpoint in Study 8.

3 ACR 20 responders at Week 24 was 1 of 4 pre-specified secondary endpoints without multiplicity adjustments in Study 8.

4 For the Week 24 ACR 50 and ACR 70 responder analyses, if patients met early escape criteria at Week 16 for the placebo and golimumab50 groups, the ACR component value at Week 24 was replaced with the corresponding component value at Week 16.

5 The DAS 28 (CRP) is an assessment of disease activity and it includes tender joints (maximum is 28), swollen joints (maximum is 28), CRP, and patient's assessment of disease activity. For the DAS28 (CRP) score, treatment failure rules were not applied and there was no missing data imputation. For patients who met early escape criteria at Week 16 for the placebo and golimumab50 groups, non-missing DAS component values at Week 24 were replaced with the corresponding values at Week 16.

AS:

Study T09:

Primary endpoint: ASsessment in Ankylosing Spondylitis (ASAS) 20 Response at Week 14

An ASAS 20 response (Anderson et al, 2001) was defined as:

(1) An improvement of ≥ 20% from baseline and an absolute improvement from baseline of at least 1 on a 0 to 10 cm scale in at least 3 of the following 4 domains:

- Patient global assessment
- Pain (total back pain) assessment
- BASFI (Bath Ankylosing Spondylitis Functional Index) score
- Inflammation (average of the first 2 questions of the BASDAI 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

AS Efficacy Results (provided by Dr. Brodsky):

Golimumab 50 mg and golimumab 100 mg are effective in reducing signs and symptoms of AS. Large treatment effects of golimumab were observed compared to placebo (Table 2.2.2.3). The pre-specified sign and symptom primary efficacy endpoints are highlighted in yellow.

Table 2.2.2.3: Major Signs and Symptom Results in the AS Study (i.e., Study 9)

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

1 Patients may have been taking stable doses of concomitant MTX, HCQ, SSZ, NSAIDs, and/or oral corticosteroids equivalent to ≤ 10 mg prednisone/day during the study. Golimumab50 is golimumab 50 mg SC given once every 4 weeks and golimumab100 is golimumab 100 mg SC given once every 4 weeks.

2 The primary efficacy endpoint in Study 9 was the proportion of patients with an ASAS 20 response at Week 14.

3 The proportion of patients with an ASAS 20 response at Week 24 was 1 of 3 pre-specified secondary endpoints without multiplicity adjustments.

4 ASAS 5/6 responders achieved a 20% improvement from baseline in 5 of the following 6 domains: total back pain (VAS 0 to 10 cm), patient global (VAS 0 to 10 cm), function (BASFI score), the mean morning stiffness score in the BASDAI (VAS 0 to 10 cm), CRP, and spine mobility (lumbar side flexion).

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Safety:

Treatment with golimumab was generally well tolerated in patients with RA, PsA, or AS. The types of clinically important AEs were generally similar to those reported for other anti-TNF agents (Tables 2.2.2.4 and 2.2.2.5).

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Table 2.2.2.4. Deaths, SAEs, DAEs1, AEs, Serious Infections, & Malignancies through Week 24.[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	placebo	golimumab50	golimumab100	placebo to golimumab50	golimumab50 to golimumab100
Treated patients	639	683	977	205	109
Mean duration of follow-up	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
Deaths, SAEs, AEs leading to discontinuation (DAEs), & AEs					
≥ 1 Death, n (%)	1 (0.2%)	1 (0.1%)	2 (0.2%)	0 (0%)	0 (0%)
≥ 1 SAE	7%	5%	6%	3%	4%
≥ 1 DAE	4%	3%	3%	1%	0%
AEs	70%	75%	75%	45%	39%
Adverse Events of Interest					
Serious infection	2%	2%	2%	1%	0%
All Malignant Neoplasms	0.8%	0.3%	1.1%	0%	0%
All Malignant Neoplasms (except NMSC)	0.5%	0.1%	0.5%	0%	0%
NMSC	0.3%	0.1%	0.6%	0%	0%
Anaphylactic reactions or serum sickness	0.2%	0%	0%	0%	0%

[1] Double-blind, controlled portions of 5 Phase 3 Trials. Patients may appear in more than 1 column.

Table 2.2.2.5. SAEs through Week 24 in 5 Phase 3 Studies.[1]

	Treatment Groups Assigned at Randomization			Escape Treatment Groups	
	placebo	golimumab50	golimumab100	placebo to golimumab50	golimumab50 to golimumab100
Treated patients	639	683	977	205	109
Mean duration of follow-up	21 weeks	22 weeks	24 weeks	8 weeks	8 weeks
Mean # of SC administrations	5.0	5.5	5.8	2.0	2.0
n (%) patients with ≥ 1 SAE	**43 (7%)**	**35 (5%)**	**54 (6%)**	**6 (3%)**	**4 (4%)**
Sepsis, %	0%	0%	0.6%	0%	0%
Cellulitis, %	0%	0.1%	0.4%	0%	0%
Pneumonia, %	0.6%	0.3%	0.3%	0%	0%
Skin infection, %	0%	0%	0.3%	0%	0.2%
URI, %	0%	0%	0.3%	0%	0%
UTI, %	0.3%	0.1%	0.2%	0.5%	0%
Anemia, %	0.3%	0%	0.2%	0%	0.9%
Pneumonitis, %	0.2%	0%	0.2%	0%	0%
Chest pain, %	0%	0%	0.2%	0.5%	0%
Arthritis bacterial, %	0%	0%	0.2%	0%	0%
Hepatitis, %	0%	0%	0.2%	0%	0%
Abdominal pain upper, %	0%	0%	0.2%	0%	0%
Depression, %	0%	0%	0.2%	0%	0%
Rheumatoid arthritis, %	0.6%	0.1%	0.1%	0.5%	0%
Colitis, %	0.3%	0.1%	0.1%	0%	0%
Myocardial infarction, %	0.3%	0.1%	0.1%	0%	0%
Vomiting, %	0%	0.3%	0%	0%	0%
Basal cell carcinoma, %	0.3%	0%	0%	0%	0%

[1] Controlled portions. SAEs by preferred term (≥ 2 SAEs occurred in any group). Patients may appear in more than 1 column

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2.2.3 What pharmacodynamic markers were evaluated?

Select markers of inflammation including TNFα, and IL-6 were evaluated in sera from subjects with RA, PsA and AS prior to and following initiation of treatment with golimumab or golimumab + MTX. The data showed decrease of these inflammatory markers following golimumab treatment. The relationship between the reported biomarker data and mechanisms by which golimumab exerts its clinical effects have not been established.

2.2.4 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Concentrations of golimumab in serum were determined in human serum samples with validated competitive electrochemiluminescence (ECL) assay and electrochemiluminescence-based Immunoassay (EIA). See Section 2.6.1 and Appendix 4.4.

2.2.5 What was exposure-response relationship of golimumab in terms of efficacy and safety?

Dose Selection: The selected doses and dosage regimens for the Phase 3 studies in RA, PsA, and AS were golimumab 50 mg and 100 mg SC every (q) 4 weeks. These doses were chosen based on the results of nonclinical studies, a Phase 2 dose-ranging study of golimumab in subjects with RA (C0524T02), as well as Sponsor's clinical experience with infliximab (REMICADE®), another anti-TNFα mAb.

In the Phase 2 dose-finding study (C0524T02), 4 dosage regimens of golimumab (fixed doses of 50 mg and 100 mg, administered SC q2 or q4 weeks with MTX) were evaluated. The primary endpoint was 20% improvement in ACR criteria (ACR 20) at Week 16. Serum concentrations of CNTO 148 generally attained steady state by Week 12 for all treatment groups (Figure 2.2.5.1). After repeated CNTO 148 SC administrations of 50 mg q4 weeks, 50 mg q2 weeks, 100 mg q4 weeks, and 100 mg q2 weeks, the median steady-state trough concentrations were 0.48, 1.16, 1.20, and 3.37 μg/mL, respectively, and the median steady-state peak concentrations were 1.71, 3.82, 4.08, and 7.78 μg/mL, respectively.

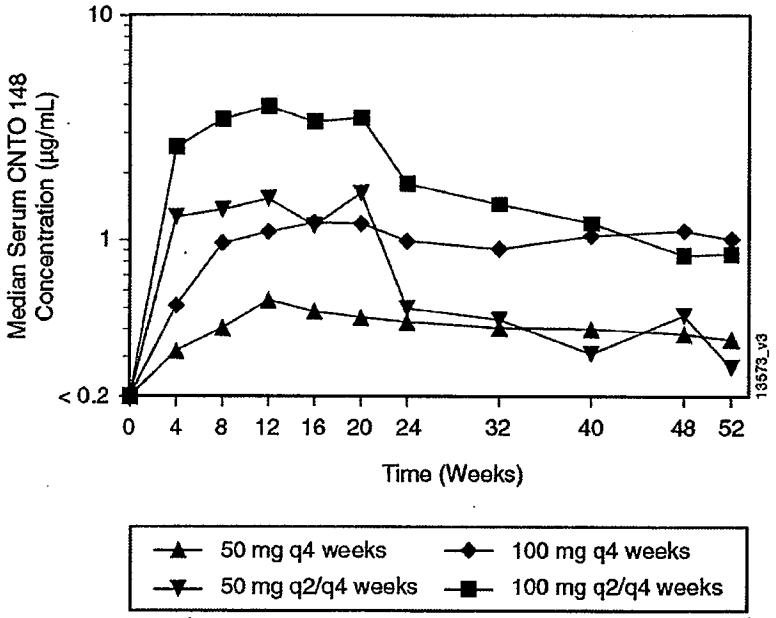

Figure 2.2.5.1. Median serum CNTO 148 trough concentration (microgram/mL) through Week 52 by visit; treated subjects.

The group receiving the lowest dosage regimen (golimumab 50 mg q4 weeks) had ACR 20, ACR 50, and ACR 70 responses that were similar to the responses associated with the 3 higher dose regimens, and no clear dose-response relationship was shown (Table 2.2.5.1).

Table 2.2.5.1. Number of subjects who achieved ACR 20, 50 and 70 response at Week 16; randomized subjects.

		CNTO 148				
	Placebo	50 mg q4 weeks	50 mg q2 weeks	100 mg q4 weeks	100 mg q2 weeks	Combined
Subjects randomized	35	35	34	34	34	137
ACR20						
n	35	35	34	34	34	137
Subjects in response	13 (37.1%)	21 (60.0%)	17 (50.0%)	19 (55.9%)	27 (79.4%)	84 (61.3%)
p-value		0.056	0.281	0.119	< 0.001	0.010

		CNTO 148				
	Placebo	50 mg q4 weeks	50 mg q2 weeks	100 mg q4 weeks	100 mg q2 weeks	Combined
Subjects randomized	35	35	34	34	34	137
ACR 50						
n	35	35	34	34	34	137
Subjects in response	2 (5.7%)	13 (37.1%)	8 (23.5%)	10 (29.4%)	11 (32.4%)	42 (30.7%)
p-value		0.001	0.036	0.009	0.005	0.003
ACR 70						
n	35	35	34	34	34	137
Subjects in response	0 (0.0%)	3 (8.6%)	5 (14.7%)	6 (17.6%)	3 (8.8%)	17 (12.4%)
p-value		0.077	0.018	0.009	0.072	0.028

All CNTO 148 plus MTX dose groups showed a decrease in CRP levels compared with placebo plus MTX. However, the magnitude of this effect was smaller in the 50 mg q4 weeks group compared with the 3 higher dose regimens (Figure 2.2.5.2).

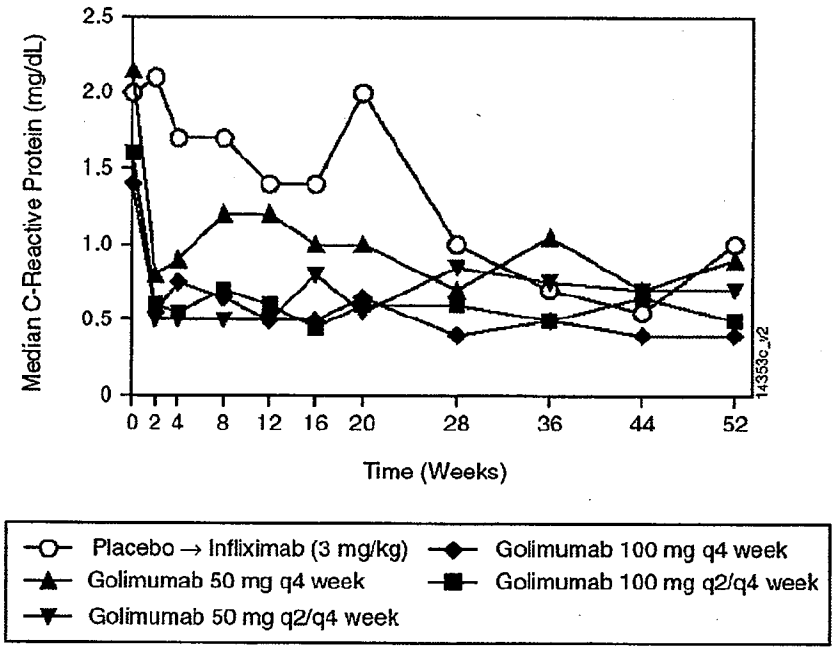

Figure 2.2.5.2. C-reactive protein levels through Week 52 following different dosage regimens of sc golimumab compared with the placebo to infliximab (3 mg/kg) group in C0524T02.

The ACR 20 response at Week 16 was maintained through Week 52 in the CNTO 148 plus MTX treatment groups even though 2 of the 4 treatment groups lowered dose frequency from q2 weeks to q4 weeks (Figure 2.2.5.3). No clear dose response was observed.

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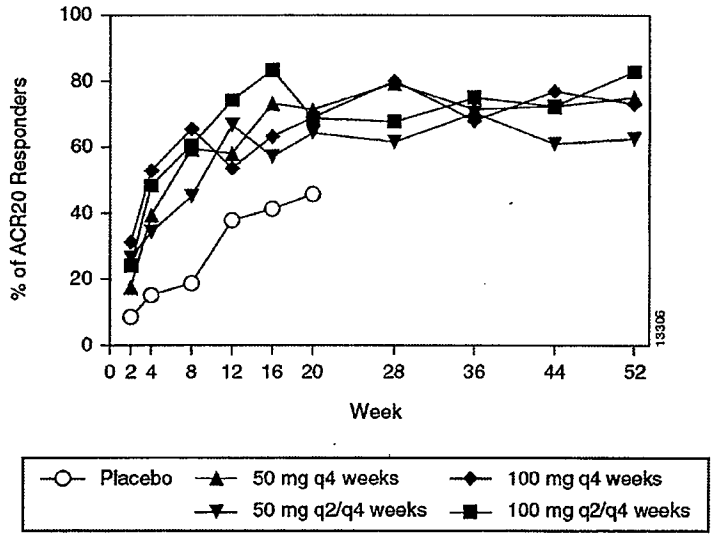


Figure 2.2.5.3. Percentage of ACR 20 responders over time; randomized subjects.

Based on these pharmacokinetic and efficacy data, CNTO 148 50 mg and 100 mg SC q4 weeks were selected for evaluation in a Phase 3 program.

As with other marketed anti-TNFα agents, specific dose-ranging studies in PsA and AS were not performed with golimumab. Dose and posology of other anti-TNFα agents (ie, etanercept, adalimumab) used in the treatment of RA have been successfully extrapolated to PsA and AS. RA, PsA, and AS are related rheumatologic diseases. The 3 subject populations have similarities, with comparable age distributions, background medications, risk:benefit relationships, and inflammatory pathophysiology. In addition, the safety profiles of anti-TNFα agents in previous studies in subjects with PsA and AS have been similar to those seen in subjects with RA. Therefore, the same 2 dosage regimens of golimumab (50 or 100 mg q4 weeks) that were selected for subjects with RA based on the results of the Phase 2 study, were also selected to evaluate efficacy and safety in subjects with active PsA and AS.

Exposure-Response for Efficacy and Safety: The efficacy and safety of two dosage regimens of golimumab (50 mg and 100 mg SC q4 weeks) were evaluated in the 5 Phase 3 studies in subjects RA, PsA, or AS. Similar to findings in the Phase 2 dose-ranging study, overall, treatment with either golimumab 50 mg or 100 mg q4 weeks showed similar efficacy (Tables 2.2.2.1, 2.2.2.2 and 2.2.2.3). The safety profiles were also similar between the two doses studied (Tables 2.2.2.4 and 2.2.2.5) and 50 mg seems safer with lower AE rates in some categories. Therefore, 50 mg was selected as the marketing dose.

2.2.6 What are PK characteristics of glimumab in healthy subjects?

The PK of golimumab was studied in both healthy subjects and RA patients after single doses. PK has also been evaluated in RA patients after multiple dosing.

Healthy Subjects-Single Dose:

Three Studies:

1. Study C0524T13 (Study 13) was an open-label, single dose, single period, in-patient/out-patient study involving 30 healthy adult male subjects. Subjects received a single SC administration of 100 mg golimumab as a liquid formulation.
2. Study C0524T23 (Study 23) was conducted to assess the PK profiles of golimumab following a single SC injection of 50 and 100 mg golimumab as a liquid formulation administered to healthy male Caucasian or Japanese subjects. 27 Caucasian subjects received a single SC injection of 50 mg (n = 14) or 100 mg (n = 13) golimumab.
3. Study C0524T24 (Study 24) was to assess the bioequivalence of a single SC injection of 100 mg golimumab, supplied as 1.0 mL sterile liquid delivered by 1 of 2 drug injection methods: 1) a single injection delivered by an autoinjector, and 2) a single injection delivered by a needle and syringe.

Pharmacokinetic parameters from these studies are listed in Table 2.2.6.1. Overall results were comparable among studies. Following single SC dosing of 50 or 100 mg to healthy subjects, median Tmax was about 4-6 days, mean golimumab apparent clearance was 12-19 mL/day/kg and mean half-life was 11-13 days. Only one study (Study 23) studied two doses and data showed that exposure increased more than double from 50 to 100 mg in Caucasians.

Table 2.2.6.1. Pharmacokinetic Parameters in Healthy Subjects (Single Dose, 50 or 100 mg).

PK Parameters	Study 13	Study 23 (Caucasian)		Study 24 (LIV)
Dose	100 mg	50 mg	100 mg	100 mg
Cmax (µg/mL)	5 ± 2	2.5 ± 1	7 ± 2	6 ± 3
Tmax (Day)*	3.5	4	4	6
AUC(0-49D) (µg*Day/mL)	80 ± 26	44 ± 15	119 ± 39	
AUC(inf) (µg*Day/mL)	84 ± 31	48 ± 17	130 ± 47	96 ± 40
CL/F (mL/Day/kg)	17 ± 6	19 ± 13	12 ± 3	15 ± 7
$T_{1/2}$ (Day)	11 ± 4	11 ± 3	13 ± 2	12 ± 3
V/F (mL/kg)	270 ± 97	262 ± 82	224 ± 49	253± 121

* Median

2.2.7 What are PK characteristics of golimumab in RA patients? Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dense PK data were collected from 2 studies in RA patients following ascending single doses: one (Study C0466T01) via IV infusion route and the other (Study C0466T02) via SC route.

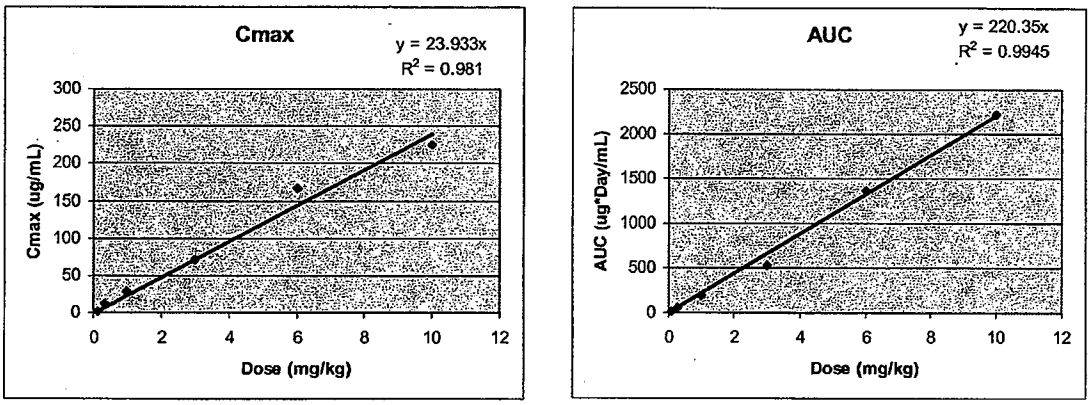
Single dose:

IV (Study 01):

Following a single IV administration, both Cmax and AUCinf of golimumab increased proportionally with dose over a range of doses from 0.1 mg/kg to 10 mg/kg (C0466T01) (Table 2.2.7.1 and Figure 2.2.7.1). Ten-fold increases in dose (0.1 mg/kg to 1 mg/kg or 1 mg/kg to 10 mg/kg) resulted in approximately 8- to 11-fold increases in mean Cmax. Similarly, 10-fold increases in dose (0.1 mg/kg to 1 mg/kg, 0.3 mg/kg to 3 mg/kg, or 1 mg/kg to 10 mg/kg) resulted in an approximately 8- to 13-fold increases in the mean AUCinf.

Table 2.2.7.1. PK Parameters in RA Subjects Receiving a Single IV dose of Golimumab.

PK Parameters	0.1 mg/kg (n=3)	0.3 mg/kg (n=3)	1 mg/kg (n=4)	3 mg/kg (n=5)	6 mg/kg (n=4)	10 mg/kg (n=4)
Cmax (µg/mL)	2.6 ± 0.3	12 ± 4	28 ± 4.5	71 ± 19	167 ± 42	225 ± 35
AUC(inf) (µg*Day/mL)	15 ± 2	66 ± 19	196 ± 54	524 ± 179	1344 ± 659	2222 ± 1491
CL (mL/Day/kg)	6.6 ± 1	5 ± 1.7	5 ± 1	6 ± 2	5 ± 2	6.7 ± 5
$T_{1/2}$ (Day)	8 ± 5	12 ± 7	8 ± 2	13 ± 4	16 ± 4	20 ± 13
V (mL/kg)	77 ± 38	77 ± 41	58 ± 15	112 ± 40	121± 50	126 ± 22



a) Cmax b) AUC

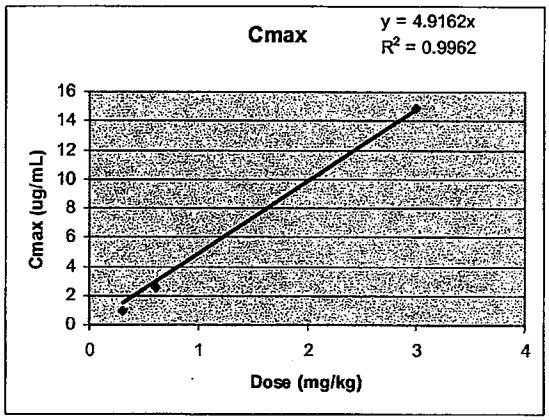
Figure 2.2.7.1. Relationship between Dose (0.1 to 10 mg/kg) and Cmax (a) and AUC (b).

SC (Study 02):

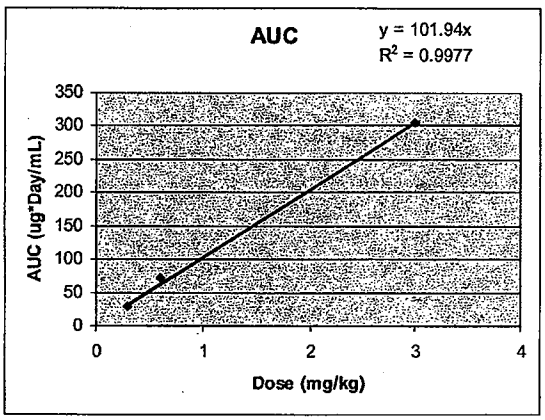
Following a single SC administration, both Cmax and AUCinf appeared to increase proportionally with the dose at 0.3, 0.6, and 3.0 mg/kg (C0466T02) (Table 2.2.7.2 and Figure 2.2.7.2). However, relative lower Cmax and AUC values were observed following a single SC administration of 1.0 mg/kg dose. No clear separation was observed in systemic exposure between 0.6 mg/kg and 1.0 mg/kg after a single SC administration.

Table 2.2.7.1. PK Parameters in RA Subjects Receiving a Single SC dose of Golimumab.

PK Parameters	0.3 mg/kg (n=2)	0.6 mg/kg (n=5)	1 mg/kg (n=5)	3 mg/kg (n=5)
Cmax (µg/mL)	1 ± 0.2	2.6 ± 2	2 ± 1	15 ± 9
AUC(inf) (µg*Day/mL)	29 (n=1)	71 ± 48	65 ± 60	304 ± 156
Median Tmax (Day)	5	3	3	2
CL/F (mL/Day/kg)	6.6 ± 1	5 ± 1.7	5 ± 1	6 ± 2
$T_{1/2}$ (Day)	8 ± 5	12 ± 7	8 ± 2	13 ± 4
V/F (mL/kg)	245 (n=1)	214 ± 84	737 ± 335	408 ± 334



a) Cmax



b) AUC

Figure 2.2.7.1. Relationship between Dose (0.1 to 3 mg/kg) and Cmax (a) and AUC (b).

Absolute Bioavailability (SC vs. IV):

Based on a cross-study comparison of mean AUC_{inf} data at dose levels of 0.3 mg/kg and 3.0 mg/kg from studies C0466T02 (SC) and C0466T01 (IV), the absolute bioavailability of golimumab after a SC administration was estimated to be 44% and 58%, respectively. The data from the single-dose 1.0 mg/kg cohort were not included for bioavailability estimation since this cohort was deemed to be an outlier. The ratio of mean dose-normalized AUCinf (SC vs IV) was 53%.

Multiple Doses:

When golimumab was administered at 50 mg or 100 mg q4 weeks, serum golimumab concentrations generally reached steady state by Week 12. The attainment of steady state by

Week 12 is in agreement with the PK prediction based on the typical $T_{1/2}$ value of approximately 2 weeks following single doses.

Because the typical $T_{1/2}$ of golimumab at 50 or 100 mg dose is approximately 2 weeks and golimumab is given q4 weeks, the accumulation index (the ratio of AUC over a dosing interval at steady state and after single dose) is predicted to be 1.3. The mean ratio of the observed trough serum concentration at steady state (eg, Week 12) over the trough concentration at Week 4 (ie, after the 1st dose) was approximately 1.4 (range: 0.9 to 2.1), which was aligned with the predicted accumulation index. In addition, trough serum concentration was maintained at similar levels after reaching steady state, indicating that the PK of golimumab is time independent once steady state is reached.

POP-PK analysis was conducted based on data obtained from 4 Phase 3 studies (2 for RA, 1 for PsA and 1 for AS). Typical PK parameters for RA, PsA and AS are listed in Table 2.2.7.3.

Table 2.2.7.3. Summary of typical population PK parameters in the three disease populations (RA, PsA, and AS).

Population PK Parameter Estimate (95% CI)[a]	RA	PsA	AS
CL/F (L/day)[b]	1.91 (1.80-2.03)	1.38 (1.30-1.47)	1.41 (1.31-1.51)
V/F (L)[b]	26.7 (24.5-28.7)	24.9 (22.7-26.9)	22.6 (20.7-24.4)
Ka (1/day)	0.668 (0.564-0.875)	0.908 (0.701-1.170)	1.010 (0.760-1.460)

[a]Typical population PK parameters estimated by NONMEM with the original final population PK dataset, and 95% confidence intervals calculated using 1,000 re-sampled and successfully converged bootstrapping runs are presented.
[b]Based on standardized weight of 70 kg

2.2.8 How does the PK of golimumab in healthy volunteers compare to that in RA, PsA or AS patients?

Golimumab appeared to show higher clearance in healthy subjects than in RA subjects based on dense PK data (Table 2.2.8.1). PK between healthy subjects and RA may be confounded by inter-study variability, disease state, concomitant medications or small sample size. Methostrexate is shown to decrease golimumab clearance. However, apparent clearance in healthy subjects was more similar to derived values based on POP-PK analysis in RA subjects.

Subjects with RA generally had lower serum golimumab concentrations (higher apparent clearance) than subjects with either PsA or AS who were treated with similar dose regimens. This became more notable for subjects with RA who were MTX-naïve (C0524T05) or who were previously treated with at least 1 anti-TNFα agent[s] (C0524T11) (Table 2.2.8.2). POP-PK analysis showed that RA subjects had a larger apparent clearance than PsA and AS subjects.

Table 2.2.8.1. Derived PK Parameter Comparison Between Healthy Subjects, RA, PsA and AS Subjects.

Population	Typical CL/F (70 kg) from POP-PK Analysis	Typical T1/2 from POP-PK Analysis	CL/F from dense PK data	T1/2 from dense PK data
Healthy Subjects			12-19 mL/day/kg	11-13 days
RA	+ MTX: 22.6 mL/day/kg - MTX: 27.3 mL/day/kg	+ MTX: 11.7 days - MTX: 9.7 days	10-13 mL/day/kg	12-24 days
PsA	19.7 mL/day/kg	12.5 days	N/A	N/A
AS	20.1 mL/day/kg	11.1 days	N/A	N/A

Table 2.2.8.2. Median Trough Golimumab Concentrations at Week 12.

Study Population		Golimumab 50 mg + MTX	Golimumab 100 mg + MTX
• C0524T06 (active RA despite MTX therapy)		0.57 μg/mL	0.94 μg/mL
• C0524T11 (active RA and previously treated with anti-TNFα therapy)		0.35 μg/mL	0.91 μg/mL
• C0524T05 (active RA and naïve to MTX therapy)		0.35 μg/mL	0.63 μg/mL
C0524T08	PsA	0.46 μg/mL	0.94 μg/mL
C0524T09	AS	0.65 μg/mL	1.34 μg/mL

See PM Review (Appendix 4.3) for POP-PK related analyses.

2.2.9 What are transport characteristics of golimumab in animals?

Golimumab was shown to cross the placenta into developing fetuses. Fetal exposure to golimumab was proportional to the increase in SC dose administered to the dams.

Excretion of golimumab into breast milk was also observed. The excretion of golimumab in milk was negligible when compared to serum golimumab concentrations in dam cynomolgus monkeys.

Refer to Dr. Bond's (Pharm/Tox) review for details.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Population PK and covariate analyses were conducted with Phase 3 study data to determine the effect of subject weight, age, gender, race, baseline disease characteristics [e.g., disease duration, baseline disease activity index score (CRP, DAS28)], baseline renal function [creatinine clearance (CRCL)], baseline hepatic functions [eg, AST, ALT, ALB], comorbidities (past or current diagnosis of diabetes, hypertension, and hyperlipidemia), and immune response (IR, ie antibodies to golimumab) on golimumab PK parameters. A separate PK study was conducted in Caucasian and Japanese healthy subjects to determine the race difference in golimumab PK (Study 23).

The clinical studies of golimumab did not enroll pregnant or lactating women, or pediatric subjects.

Although no specific PK studies were conducted, based on the results of the POP-PK analyses, body weight was the most significant covariate identified for both CL/F and V/F of golimumab (Figure 2.3.1.3). Age and race did not appear to impact on the PK of golimumab in adult RA PsA, and AS patients (Figures 2.3.1. 2 and 2.3.1.5). Population PK analysis suggested no PK difference between genders after body weight adjustment in RA and PsA patients. In AS study, gender was a significant covariate based on covariate analysis and females showed 13% higher apparent clearance than males after body weight adjustment (Figure 2.3.1.1). Refer to PM review (Appendix 4.3) for POP-PK and covariate analyses.

a) Gender

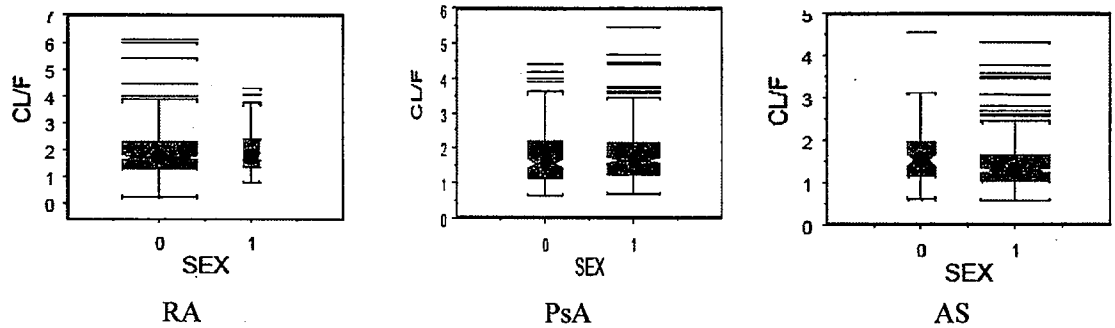


Figure 2.3.1.1. Empirical Bayesian Estimates of CL/F by Gender (0=Female, 1=Male).

b) Elderly

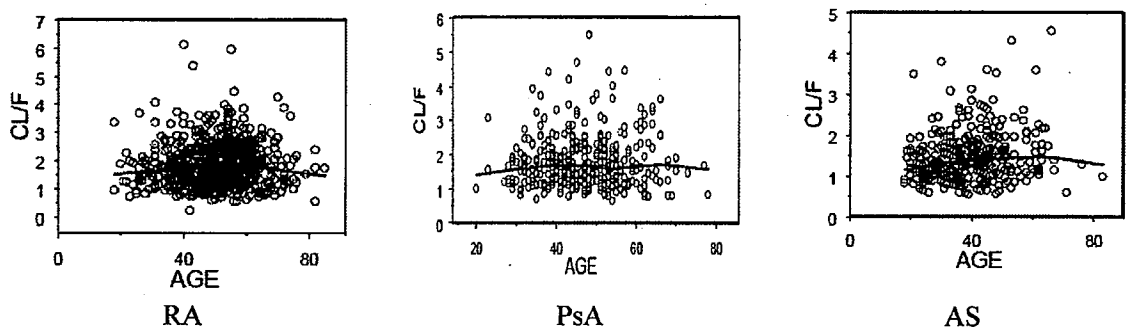


Figure 2.3.1.2. Empirical Bayesian Estimates of CL/F by Age.

c) Pediatric Patients

No studies were conducted in pediatric patients. The Sponsor requested a deferral for studying safety and efficacy in pediatric RA and PsA patients (2-16 years). They also requested waiver for pediatric RA and PsA patients (< 2 years) and waiver for pediatric studies in AS patients.

d) Body Weight

Based on the results of the POP-PK analyses, body weight was the most significant covariate identified for both CL/F and V/F of golimumab. Subjects with heavier weight tended to have higher CL/F (Figure 2.3.1.3) and larger V/F.

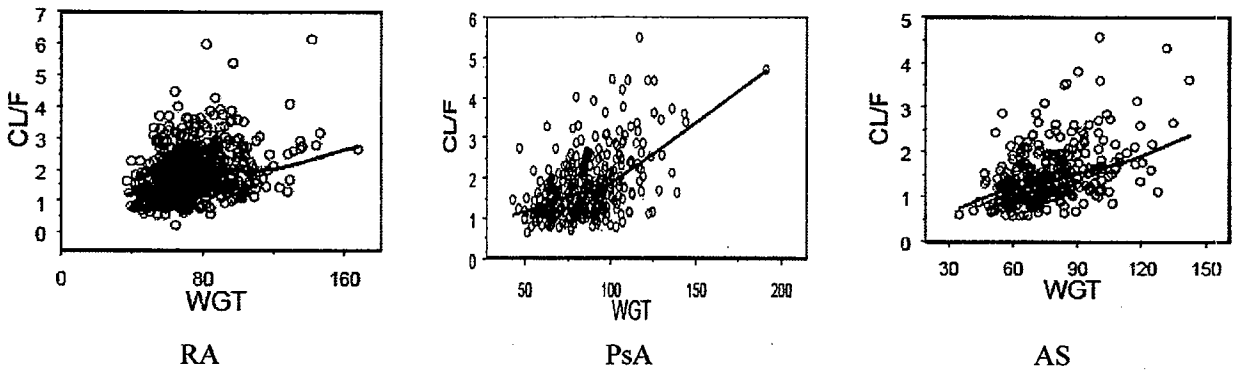


Figure 2.3.1.3. Empirical Bayesian Estimates of CL/F by Body Weight.
(Locally weighted scatter plot smoother [LOESS] trend lines are overlaid in the scatter plots)

The Empirical Bayesian Estimates (EBEs) of CL/F were also compared by weight quartiles (Figure 2.3.1.4). The results showed that post hoc estimates of CL/F largely overlapped for subjects in different weight quartile groups.

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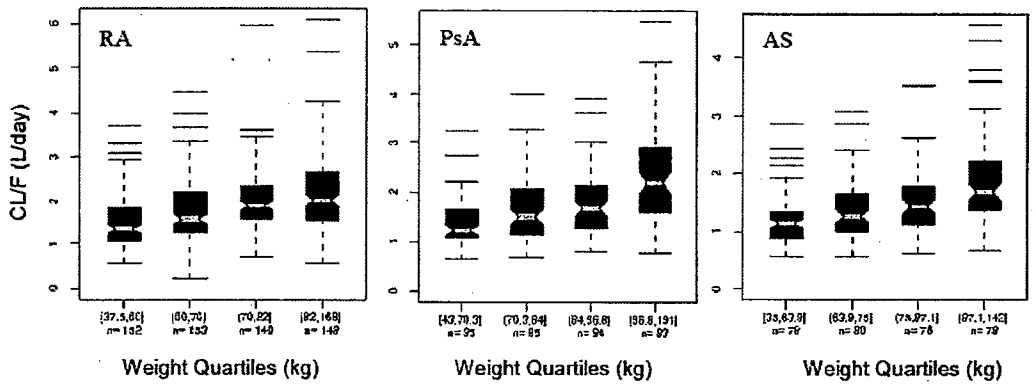


Figure 2.3.1.4. Empirical Bayesian estimates of CL/F by weight quartiles in subjects with RA, PsA or AS.

To illustrate the impact of weight on CL/F, a comparison of median EBEs of CL/F between subjects who were ≤ 100 kg and > 100 kg in the RA, PsA, and AS populations are shown in Table 2.3.1.1.

Table 2.3.1.1. Comparison of median (interquartile range) empirical Bayesian estimates of CL/F in subjects with RA, PsA, or AS whose weights were ≤ 100 kg and > 100 kg.

	RA		PsA		AS	
	n	CL/F[a] (L/day)	n	CL/F[a] (L/day)	n	CL/F[a] (L/day)
Subjects ≤100 kg	543	1.68 (1.26-2.26)	267	1.50 (1.15-1.91)	275	1.28 (1.01-1.67)
Subjects > 100 kg	50	2.09 (1.50-2.64)	70	2.33 (1.62-3.06)	37	1.76 (1.50-2.26)
CL/F difference (%)[b]		24.4%		55.3%		37.5%

[a] CL/F: median (interquartile range) values are shown

[b] Calculated as the difference of median CL/F values between subjects > 100 kg and ≤ 100 kg, expressed as percentage

e) Race

There were 474 (79.7%) Caucasians, 77 (12.9%) Asians, 5 (0.8%) Blacks, and 38 (6.3%) subjects of other races in the RA dataset (n = 594); 326 (96.7%) Caucasians, 7 (2.0%) Asians, 2 (0.5%) Blacks and 2 (0.5%) subjects of other races in the PsA dataset (n = 337), and 229 (73.3%) Caucasians, 76 (24.3%) Asians, 3 (0.9%), Blacks and 4 (1.2%) subjects of other races in the AS dataset (n = 312). There seem to have adequate numbers of Asian subjects in the RA and AS datasets for assessing the potential PK differences between Asians and Caucasians. Based on covariate analysis, race was not a significant covariate for either CL/F or V/F between Asians and Caucasians in the RA and AS populations.

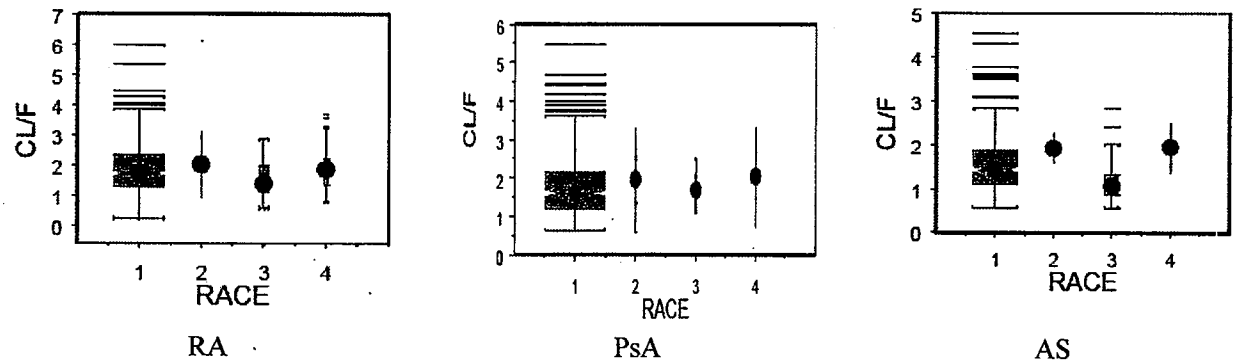


Figure 2.3.1.5. Empirical Bayesian Estimates of CL/F by Race (1=Caucasian, 2=Black, 3=Asian, 4=Other).

In addition, a Phase 1 PK study (Study 23) was conducted to assess the PK profiles of golimumab following a single SC injection of 50 and 100 mg golimumab as a liquid formulation administered to healthy male Caucasian or Japanese subjects.

A total of 51 subjects participated in the study. Twenty-four Japanese subjects received a single SC injection of either 50 mg (n = 12) or 100 mg (n = 12) golimumab, while 27 Caucasian subjects received a single SC injection of 50 mg (n = 14) or 100 mg (n = 13) golimumab. The mean weights for the Caucasian groups (70.3 and 70.9 kg for the 50 and 100 mg groups, respectively) were slightly higher than those for the Japanese groups (65.3 and 65.1 kg for the 50 and 100 mg groups, respectively).

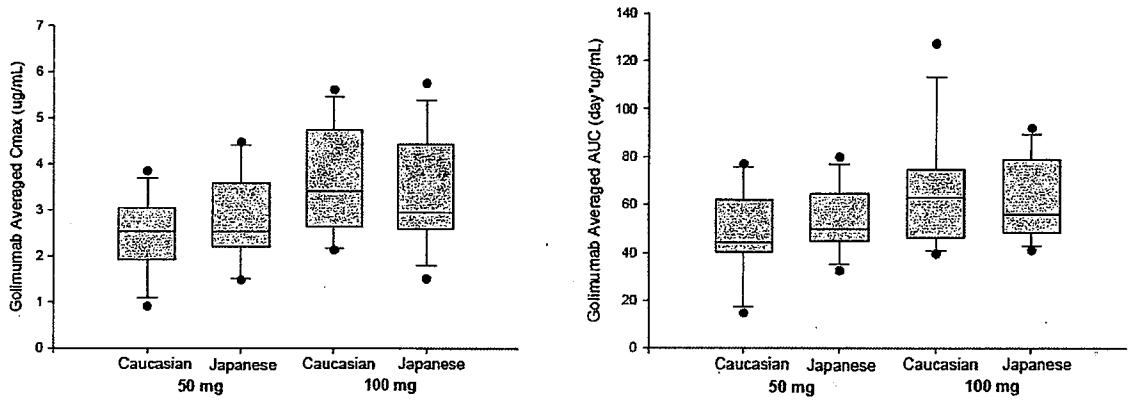
No apparent differences in PK parameters were observed between Caucasian and Japanese subjects at the same dose levels (Table 2.3.1.2 and Figure 2.3.1.6).

Table 2.3.1.2. Summary of Mean (± SD) Pharmacokinetic Parameters for Each Treatment Group.

Treatment Group (N)	AUC(0-∞) (µg·day/mL)	AUC(0-49D) (µg·day/mL)	Cmax (µg/mL)	Tmax (day)	t1/2 (day)
50 mg Japanese (12)	53.25 ±13.06	49.64 ±12.17	2.82 ±0.97	5.51 ±1.90	11.92 ±2.32
50 mg Caucasian (10) [a]	47.69 ±17.49	44.49 ±15.04	2.48 ±0.77	4.82 ±1.78	11.06 ±2.69
100 mg Japanese (12)	121.63 ±33.89	112.54 ±29.61	6.72 ±2.35	4.00 ±1.95	12.56 ±2.41
100 mg Caucasian (12)	129.72 ±47.12	118.61 ±39.09	7.21 ±2.31	4.25 ±1.55	13.28 ±2.31

Notes: SD = standard deviation.

[a] N = 11 for Cmax and Tmax.



Cmax AUC(0-∞)

Figure 2.3.1.6. Dose-Normalized Cmax (Left) and AUC(0-∞) (6B) between Caucasian and Japanese Subjects after Single Subcutaneous Administration at 50 mg and 100 mg.

f) Renal and Hepatic Impairment

The majority of the subjects with RA, PsA or AS had normal renal function. The estimated mean baseline levels of CrCL were 108.5 mL/min (range: 32.2 to 278.4 mL/min) for the 594 subjects in the RA dataset, 122.2 mL/min (range: 50.6 to 258.8 mL/min) for the 337 subjects in the PsA dataset, and 125.2 mL/min (range: 47.6 to 215.9 mL/min) for the 312 subjects in the AS dataset. The covariate analysis indicated that baseline CrCL had no significant effect on the CL/F or V/F of golimumab.

The majority of the subjects with RA, PsA, or AS had normal hepatic function (Table 2.3.1.3). The covariate analysis indicated that baseline levels of AST, ALT, and serum ALB had no significant effects on the CL/F or V/F of golimumab.

Table 2.3.1.3. Summary of hepatic function laboratory tests at baseline in subjects with RA, PsA or AS included in the population PK analysis.

	RA (n = 594)		PsA (n = 337)		AS (n = 312)	
Hepatic Function	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
ALT (U/L)	23.0 ±16.9	4-216	25.9±14.3	7-98	23.7±14.2	6-133
AST (U/L)	21.1±10.0	8-125	22.3±8.1	9-61	22.0±8.9	8-99
ALB (g/dL)	4.2±0.4	3.0-5.7	4.3±0.3	3.5-5.1	4.4±0.3	3.2-5.2

Subgroup analysis for RA efficacy:

Odds ratios and corresponding 95% CIs were calculated using pooled data for the proportion of subjects with an ACR 20 response at Week 24 for subgroups based on select demographic characteristics. A treatment benefit versus placebo was seen for subjects in the golimumab 50 mg (Figure 2.3.1.7) group, irrespective of gender, age, weight, and race with the exception of the racial subgroups of Black and Other, which had small sample sizes. Take body weight for example, Study 06, in MTX-experienced and TNF-blocker-naïve patients, did show evidence of

a reduction in clinical efficacy with increasing body weight, but this effect was not related to the dose of golimumab used (Refer to Statistical review for final analysis). The data suggested that increased exposure by increasing dose did not translate to increased efficacy. Therefore, dose adjustment based on body weight or other intrinsic factors does not seem to be necessary.

Subgroup analysis for PsA efficacy:
Odds ratios and corresponding 95% CIs were calculated for the proportion of subjects with an ACR 20 response at Week 14 for subgroups based on select demographic characteristics. A treatment benefit versus placebo was seen for subjects in the golimumab 50 mg (Figure 2.3.1.8) group, irrespective of gender, age, weight, and race with the exception of the racial subgroups of Black and Other, which had small sample sizes. Therefore, dose adjustment based on body weight or other intrinsic factors does not seem to be necessary.

Subgroup analysis for AS efficacy:
Odds ratios and corresponding 95% CIs were calculated for the primary endpoint (ie, proportion of subjects with ASAS 20 response at Week 14) for subgroups based on select demographic characteristics. A treatment benefit versus placebo was seen for subjects in the golimumab 50 mg (Figure 2.3.1.9) group, irrespective of gender, age, weight, and race with the exception of the racial subgroups of Black and Other, which had small sample sizes. Therefore, dose adjustment based on body weight or other intrinsic factors does not seem to be necessary.

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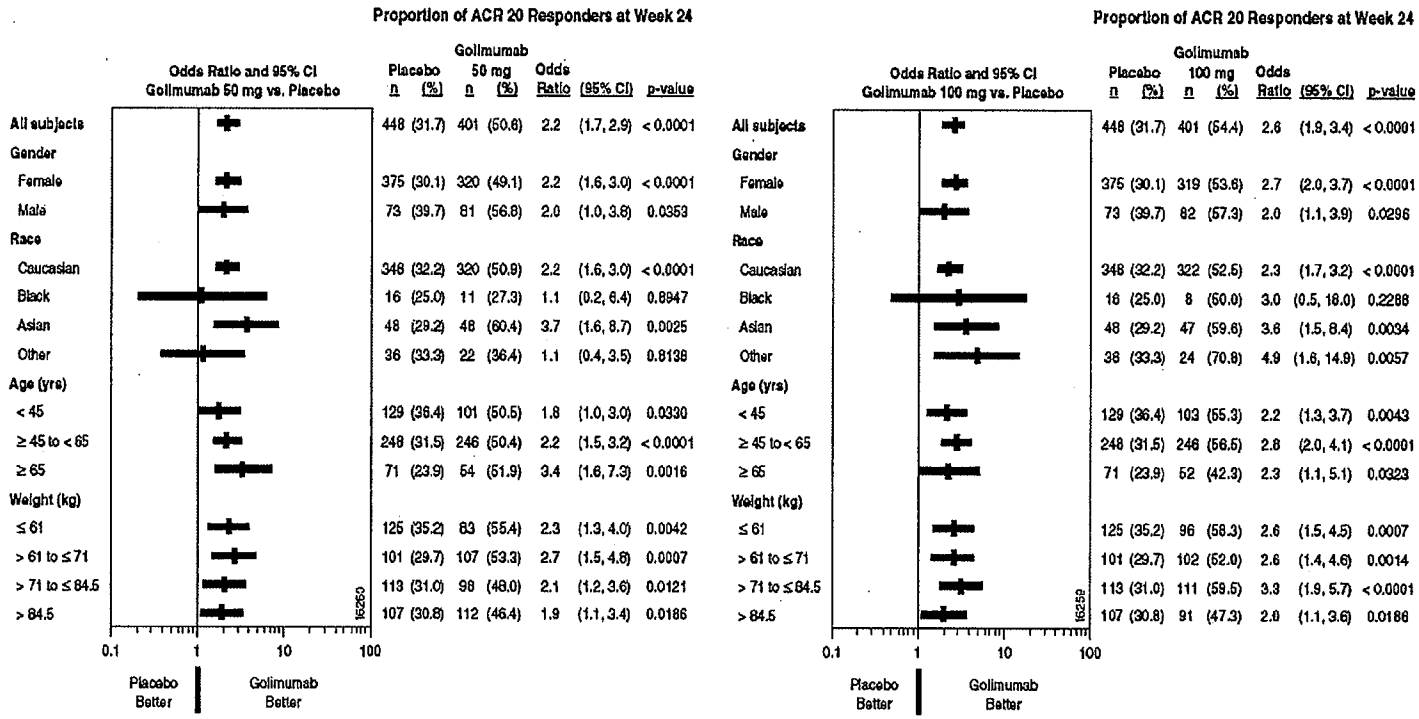

Figure 2.3.1.7. Odds ratio (vertical bars) and the 95% confidence intervals (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 24 in the golimumab 50 mg (left panel) and 100 mg (right panel) groups versus the placebo groups with or without MTX use, for subgroups defined by demographic characteristics; randomized subjects in 3 RA studies combined.

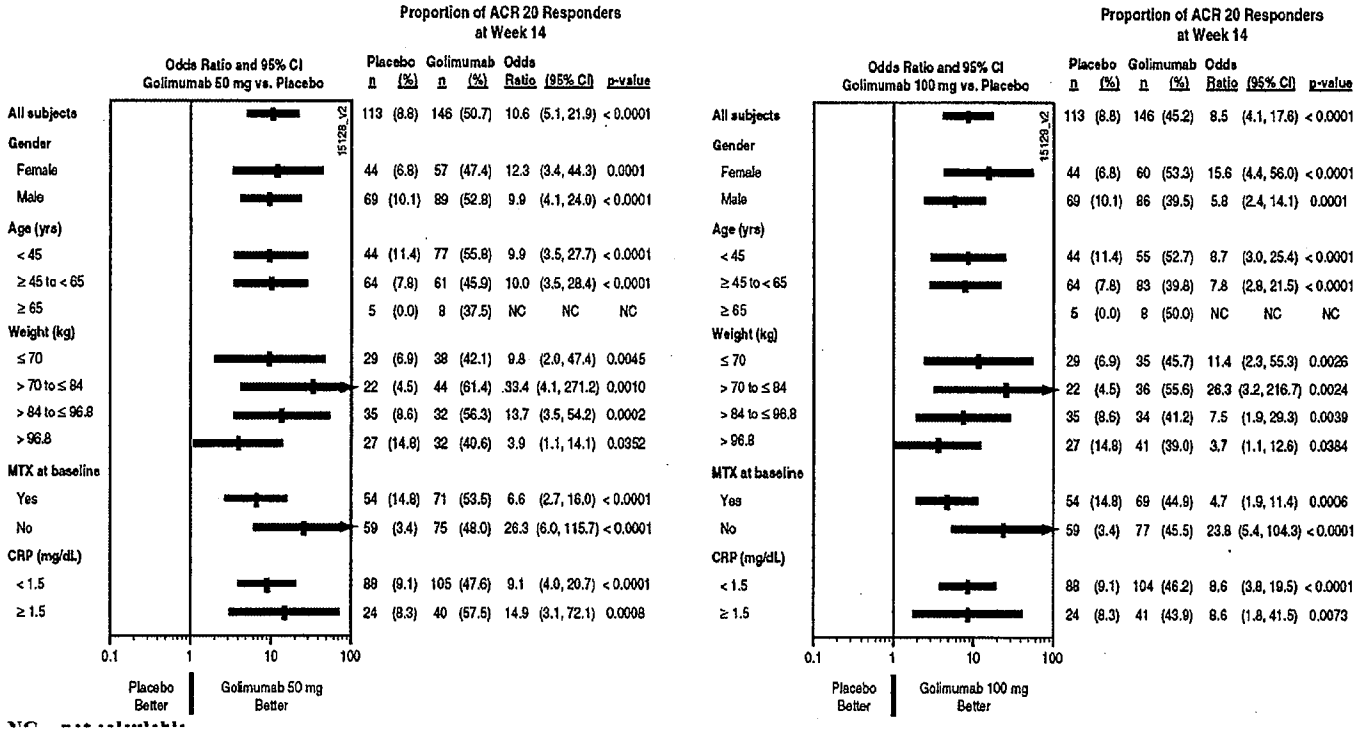

Figure 2.3.1.8. Odds ratio (vertical bars) and 95 % confidence intervals (horizontal bars) for comparing proportion of subjects who achieved ACR 20 response at Week 14 in the golimumab 50 mg (left panel) and 100 mg (right panel) groups versus the placebo groups for selected subgroups; randomized subjects.

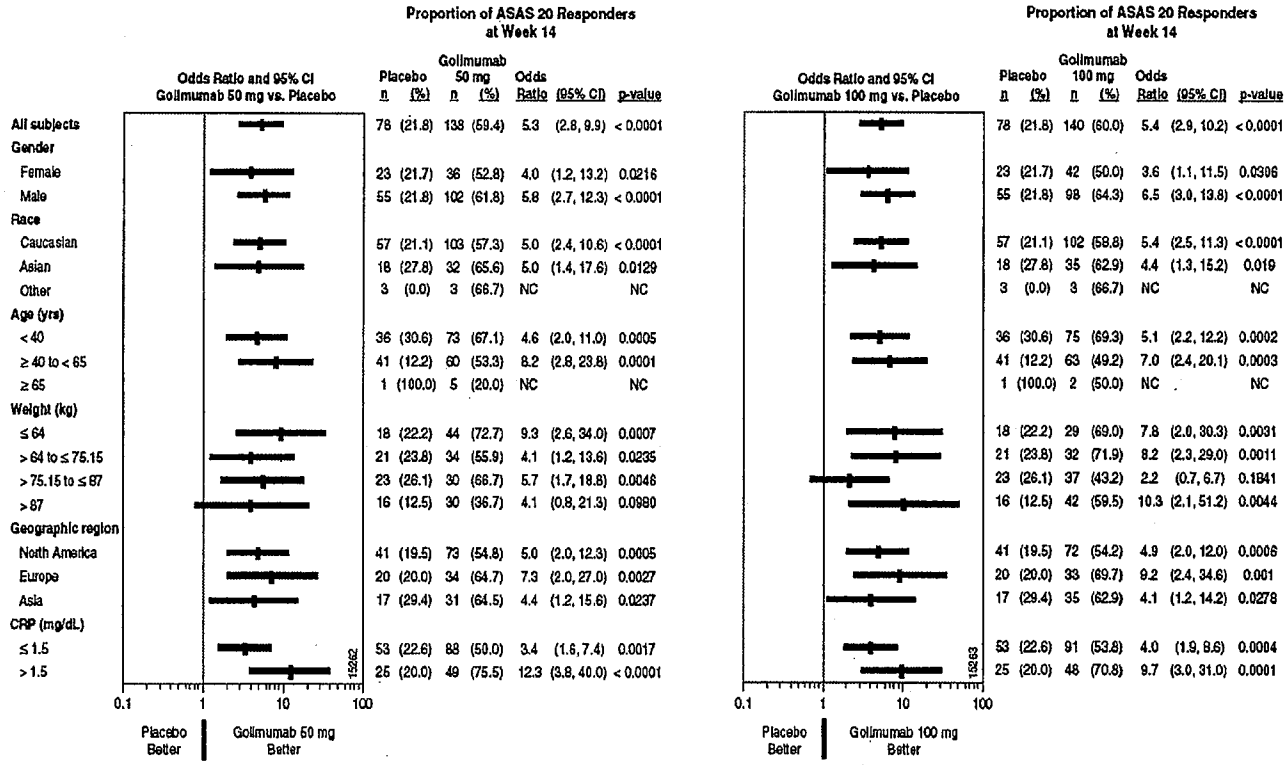

Figure 2.3.1.9. Odds ratio (vertical bars) and 95 % confidence intervals (horizontal bars) for comparing proportion of subjects who achieved ASAS 20 response at Week 14 in golimumab 50 mg group versus placebo group for selected subgroups; randomized subjects.

2.3.2 What were the immunogenicity findings for golimumab? What was the impact of immunogenicity on exposure and/or safety and efficacy?

The presence of golimumab can interfere with the detection or interpretation of an antibody response; therefore, all samples evaluated for antibodies to golimumab were also analyzed for golimumab concentration. Any subjects with positive antibody responses observed at 1 or more post treatment visits were classified as positive for antibodies to golimumab, regardless of the presence or absence of detectable golimumab in their sample(s). If the antibody to golimumab results were not positive, but there were measurable concentrations of golimumab present in the last post-treatment serum sample evaluated through the specific time period, the subject was classified as undetectable (or "inconclusive") for antibodies to golimumab.

The incidence of antibodies to golimumab through Week 24 by treatment group and combined across treatments is summarized for the 3 RA studies, and then across all 5 trials in Table 2.3.2.1.

The combined antibody to golimumab incidence across all subjects treated in Phase 3 (50 and 100 mg) was 57 of 1322 subjects (4.3%), ranging from 2.1% in C0524T06 to 6.3% in C0524T05. The data are not presented for the placebo subjects who early escaped at Week 16 to active treatment because these subjects received only 2 doses of golimumab through Week 24, and none of these subjects were positive for antibodies to golimumab. The proportion of subjects with antibodies to golimumab through Week 24 was similar across the different indications, with no notable difference in total antibody incidence between RA, PsA, and AS.

Across the 5 Phase 3 studies, the antibody incidence was similar for subjects receiving 50 mg + MTX (5 of 300, 1.7%) compared with those subjects receiving 100 mg + MTX (7 of 370, 1.9%) (Table 2.2.3.1).

Higher antibody rates were generally observed for subjects receiving golimumab in the absence of MTX based on the available data (Studies 8, 9 and 11). Across these 3 studies, the antibody incidence was 12 of 169 (7.1%) for subjects receiving 50 mg golimumab in the absence of MTX.

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Table 2.3.2.1. Summary of subjects with positive antibody to golimumab status through Week 24 by dose and methotrexate use; treated subjects in all Phase 3 studies.

	Golimumab						
	50 mg, Not Receiving MTX	50 mg + MTX	50 → 100 mg, Not Receiving MTX	50 → 100 mg + MTX	100 mg, Not Receiving MTX	100 mg + MTX	Combined
Subjects treated in C0524T05	N/A	111	N/A	N/A	110	111	332
Subjects with appropriate samples in C0524T05[a]	N/A	107	N/A	N/A	104	104	315
Subjects positive for antibodies to golimumab at any time[b]	N/A	4 (3.7%)	N/A	N/A	14 (13.5%)	2 (1.9%)	20 (6.3%)
Subjects treated in C0524T06	N/A	57	N/A	13	76	100	246
Subjects with appropriate samples in C0524T06[a]	N/A	57	N/A	12	70	97	236
Subjects positive for antibodies to golimumab at any time[b]	N/A	0 (0.0%)	N/A	0 (0.0%)	2 (2.9%)	3 (3.1%)	5 (2.1%)
Subjects treated in C0524T11	27	61	11	16	36	78	229
Subjects with appropriate samples in C0524T11[a]	24	58	11	16	32	74	215
Subjects positive for antibodies to golimumab at any time[b]	2 (8.3%)	1 (1.7%)	0 (0.0%)	2 (12.5%)	1 (3.1%)	2 (2.7%)	8 (3.7%)

	Golimumab						
	50 mg, Not Receiving MTX	50 mg + MTX	50 → 100 mg, Not Receiving MTX	50 → 100 mg + MTX	100 mg, Not Receiving MTX	100 mg + MTX	Combined
All subjects treated in RA Phase 3 studies	27	229	11	29	222	289	807
All RA subjects with appropriate samples[a]	24	222	11	28	206	275	766
Subjects positive for antibodies to golimumab at any time[b]	2 (8.3%)	5 (2.3%)	0 (0.0%)	2 (7.1%)	17 (8.3%)	7 (2.5%)	33 (4.3%)
Subjects treated in C0524T08	61	57	14	14	77	69	292
Subjects with appropriate samples in C0524T08[a]	58	56	14	14	75	68	285
Subjects positive for antibodies to golimumab at any time[b]	5 (8.6%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	7 (9.3%)	0 (0.0%)	13 (4.6%)
Subjects treated in C0524T09	91	22	18	7	112	28	278
Subjects with appropriate samples in C0524T09[a]	87	22	17	7	111	27	271
Subjects positive for antibodies to golimumab at any time[b]	5 (5.7%)	0 (0.0%)	3 (17.6%)	0 (0.0%)	3 (2.7%)	0 (0.0%)	11 (4.1%)

	Golimumab						
	50 mg, Not Receiving MTX	50 mg + MTX	50 → 100 mg, Not Receiving MTX	50 → 100 mg + MTX	100 mg, Not Receiving MTX	100 mg + MTX	Combined
All subjects treated in Phase 3 studies	179	308	43	50	411	386	1377
All subjects with appropriate samples in Phase 3 studies[a]	169	300	42	49	392	370	1322
Subjects positive for antibodies to golimumab at any time[b]	12 (7.1%)	5 (1.7%)	4 (9.5%)	2 (4.1%)	27 (6.9%)	7 (1.9%)	57 (4.3%)

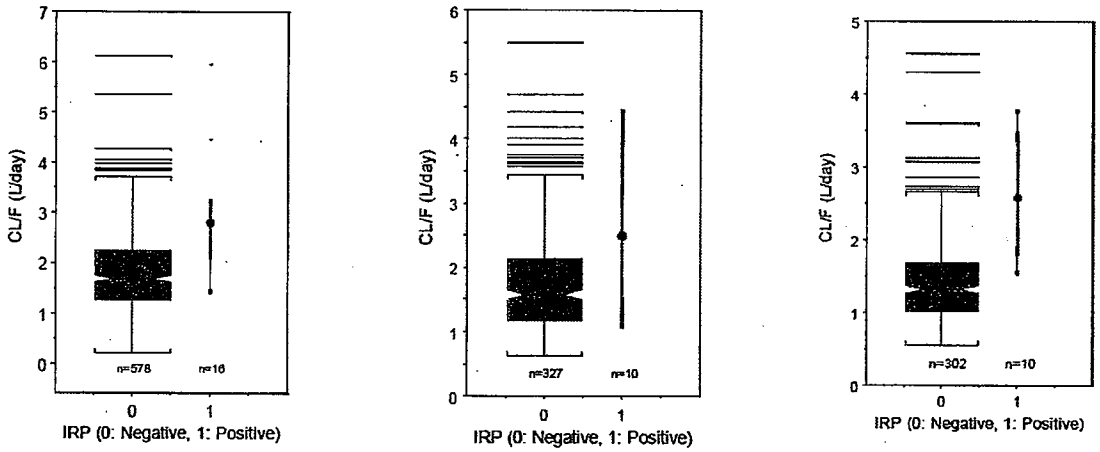
[a] Subjects with appropriate samples had 1 or more samples obtained after their first study agent administration.
[b] Includes all subjects who had at least 1 positive sample at any time.

The population PK datasets for RA (n = 594), PsA (n = 337), and AS (n = 312) contained 16, 10, and 10 subjects, respectively, who tested positive for antibodies to golimumab and yet had

measurable serum golimumab concentrations through Week 24. Additionally, 9 RA subjects (7 from C0524T05 and 2 from C0524T06), 3 PsA subjects, and 1 AS subject who tested positive for antibodies to golimumab were not included in the population PK analysis because they did not have measurable serum golimumab concentrations at one or more visits through Week 24.

Positive antibody to golimumab status (ie, positive IR status, IRP) is generally associated with lower serum golimumab concentrations across the 5 Phase 3 studies.

Although the number for subjects who tested positive was small, population pharmacokinetic analyses indicated a trend toward higher golimumab CL/F in the presence of antibodies to golimumab. The covariate analysis indicated that 1) RA subjects who were positive for antibodies to golimumab had a 29% higher CL/F as compared with all others; 2) PsA subjects who were positive for antibodies to golimumab had a 10% higher CL/F as compared with all others; and 3) AS subjects who were positive for antibodies to golimumab had a 36% higher CL/F as compared to all others (Figure 2.3.2.1).



RA PsA AS

Figure 2.3.2.1. Empirical Bayesian Estimates of CL/F by Antibody-to-Golimumab Status. (IRP: antibody-to-golimumab status [ie, immune response positive])

The small number of patients positive for antibodies to golimuma and lack of clear exposure-response in the dose/exposure range studied limit the ability to have a definitive conclusion regarding the relationship between immunogenicity and clinical efficacy and safety measures.

In the Phase 2 RA study (C0524T02), neutralizing antibodies were measured in samples from subjects classified as positive for antibodies to golimumab in the bridging EIA. Baseline (Week 0), peak EIA titer sample, and the last available positive sample from the EIA positive subjects were tested using a functional cell-based neutralization bioassay.

Eight (47%) out of 17 evaluable subjects were positive for the presence of neutralizing antibodies to golimumab (Table 2.3.2.2). A higher proportion of subjects with neutralizing antibodies were observed in the 50 mg groups relative to the 100 mg groups. The rate could be

assay dependent, i.e., reflecting differences in the sensitivity of the bridging EIA and neutralization antibody assay.

Table 2.3.2.2. Summary of neutralizing antibody to golimumab status through Week 68 (C0524T02); treated subjects.

	Golimumab				
	50 mg q4 weeks	50 mg q2/q4 weeks	100 mg q4 weeks	100 mg q2/q4 weeks	Combined
Subjects treated	37	32	33	35	137
Subjects with appropriate samples[a]	27	26	24	33	110
Subjects EIA positive for antibodies to golimumab at any time[b]	4 (14.8%)	4 (15.4%)	3 (12.5%)	8 (24.2%)	19 (17.3%)
Subjects evaluable for neutralizing antibodies[c]	3 (75 %)	4 (100%)	3 (100%)	7 (88%)	17 (89%)
Subjects positive for neutralizing antibodies[d]	3 (100%)	2 (50%)	1 (33%)	2 (29%)	8 (47%)
Subjects negative for neutralizing antibodies[d]	0 (0%)	2 (50%)	2 (67%)	5 (71%)	9 (53%)

[a] Subjects with appropriate samples had 1 or more samples obtained following their first study agent administration.
[b] Subjects EIA positive for antibodies to golimumab at any time are subjects who had at least 1 positive sample in the EIA analysis at any time. (Denominator is subjects with appropriate samples)
[c] Subjects evaluable for neutralizing antibodies are subjects who have no demonstrated interference in the neutralizing antibody assay for at least one tested sample (Denominator is subjects EIA positive for antibodies to golimumab at any time)
[d] Denominator is subjects evaluable for neutralizing antibodies

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The Sponsor did not conduct specific drug interaction studies. Disease modifying antirheumatic drugs (DMARDs, such as MTX), NSAIDs, and oral corticosteroids are commonly used for treatment of RA, PsA or AS and used in the Phase 3 studies. The effects of these selected concomitant medications on golimumab PK were evaluated in the covariate analysis with POP-PK data.

Effect of other drugs or smoking on golimumab:

a) MTX

In the RA population PK dataset 65.9% of subjects (392) were received MTX. Approximately 49% of subjects (n = 165) in the PsA population PK dataset were receiving concomitant MTX at baseline. Approximately 20% of subjects (n = 64 of 312) in the AS population PK dataset received MTX.

Similar to what has been observed with other TNFα inhibitors, the presence of MTX decreased apparent CL for golimumab. Mean trough levels at steady-state in the presence of MTX were approximately 33%, 25%, 67% higher than those in the absence of MTX in AS, PsA, and RA patients, respectively. The covariate analysis showed that concomitant use of MTX was a

significant covariate for apparent CL/F in RA subjects but not in PsA and AS subjects. The results show that MTX reduced golimumab CL/F by 17.1% in the RA population PK analysis.

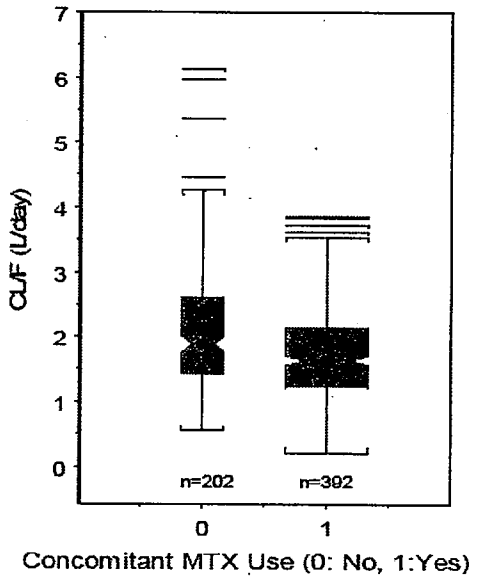


Figure 2.4.1.1. Comparison of empirical Bayesian estimates of golimumab CL/F in RA subjects with and without concomitant use of MTX. The width of the box is proportional to the sample size.

b) Other DMARDs

Two other DMARDs, sulfasalazine (SSZ), and hydroxychloroquine (HCQ) were allowed in the Phase 3 AS study (C0524T09). Eighty-three (26.6%) subjects received SSZ, and 3 (0.9%) subjects received HCQ in the AS dataset (n = 312). The covariate analysis showed that, concomitant use of SSZ did not significantly influence CL/F in subjects with AS. The effect of HCQ on golimumab PK could not be assessed due to the limited number of subjects receiving HCQ.

c) NSAID

Five hundred (84.1%) subjects in the RA dataset (n = 594), 251 (74.4%) subjects in the PsA dataset (n = 337), and 277 (88.7%) subjects in the AS dataset (n = 312) received treatment with NSAIDs. The covariate analyses showed that, concomitant use of NSAIDs did not significantly influence CL/F in any of the RA, PsA, and AS population.

d) Oral Corticosteroids

Three hundred thirty two (55.8%) subjects in the RA dataset (n = 594), 53 (15.7%) subjects in the PsA dataset (n = 337), and 50 (16.0%) subjects in the AS dataset (n = 312) received treatment with oral corticosteroids. The covariate analyses showed that, concomitant use of oral corticosteroids did not significantly influence CL/F in any of the RA, PsA, and AS population.

e) Smoking:

There were 123 (20.7%), 61 (18.1%), and 114 (36.5%) current smokers in the RA (n = 594), PsA (n = 337), and AS (n = 312) datasets, respectively. Smoking status was found to be significant covariate for CL/F in the PsA population, but not in the RA and AS populations. Subjects with PsA who were smokers had an estimated 13% higher CL/F of golimumab compared with nonsmoking subjects. Because of lack of exposure-response in the dose range studied (50-100 mg), 13% change in apparent clearance is not likely to be clinically significant.

Smoking is known to induce CYP1A2-mediated drug metabolism for small molecular drugs. The mechanism by which smoking may influence the disposition of monoclonal antibodies remains unclear.

Effect of golimumab on other drugs:

P450 Substrate Drugs:
Golimumab might indirectly influence the expression level of CYP P450 enzymes leading to altered P450 activities in patients because TNFα is known to reduce the expression level of multiple CYP P450 enzymes including CYP3A4. Golimumab inhibits effects of TNFα, presumably including the CYP down-regulatory activities of TNFα. Therefore, an indirect effect of golimumab on the expression levels of CYP enzymes appears to be possible. Upon initiation or discontinuation of golimumab, the P450 levels may increase or decrease leading to altered P450 activities. Therefore, drug interaction of golimumab with P450 substrate drugs caused by the modulation of P450s is anticipated.

The drug interactions may have clinical implication for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted based on response measurements (e.g., warfarin) or drug monitoring (e.g., cyclosporine or theophylline) where a decrease of up to 50% could become clinically relevant. The drug interactions may also have clinical implication for P450 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives.

A drug interaction study is recommended to further understand the drug interaction potential (See Section 1.2).

2.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.5 General Biopharmaceutics

2.5.1 What is the final-to-be marketed formulation (drug substance and drug product) of golimumab?

The drug substance is produced from a [redacted] cell line [redacted] The CNTO 148 PFS formulation is composed of 100 mg/mL CNTO 148 with excipient concentrations of 5.6 mM L-histidine, 4.1% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80, pH 5.5. A 50 mg/syringe (0.5 mL) is the final to-be-marketed dosage form. The final product will be liquid formulation of golimumab in a prefilled syringe (PFS) [redacted] or the same PFS in an autoinjector.

b(4)

2.5.2 What are the major development processes for drug substance and formulations for drug product? Which batches were used in the pivotal clinical and bioavailability studies?

During the development program of golimumab, changes have been made to the manufacturing processes of both drug substance and drug product. Various comparability studies have been conducted to compare different drug products.

For earlier clinical studies [redacted] produced from a cell line [redacted]

b(4)

For clinical studies [redacted] material was derived from a cell line [redacted]

b(4)

Table 2.5.2.1. Overview of the Different Formulations and Respective Clinical Studies.

	Formulation	Description	Clinical Studies
1	[redacted]	[redacted] A lyophilized formulation for IV and SC administration. The formulation was supplied as a sterile, lyophilized powder in a glass vial containing 100 mg of golimumab per vial. Each single-use vial was reconstituted with 1 mL of sterile water for injection resulting in 100 mg/mL golimumab, 10 mM sodium phosphate, 8.5% (w/v) sucrose and 0.001% (w/v) polysorbate 80 (PS 80) at pH 6.0. No preservatives were added	C0466T01 and C0466T02

b(4)

Ex. 2053-044

2	[redacted]	[redacted] A similar lyophilized formulation used golimumab produced for SC administration in Phase 2 clinical studies. The sterile, lyophilized powder was supplied in a single-use glass vial containing 100 mg/mL golimumab per vial. After reconstitution with 1 mL of sterile water for injection, each vial contained 100 mg/mL of golimumab, 10 mM sodium phosphate, 8.5% (w/v) sucrose and 0.01% (w/v) PS 80 at pH 6.0. No preservatives were added.	C0524T01, C0524T02, and C0524T03,
3	[redacted]	A liquid formulation was developed for Phase 3 studies as well as the intended commercial presentation. Golimumab in the liquid formulation was produced from cell line [redacted] Each single-use vial containing 100 mg/mL of golimumab, 5.6 mM histidine, 4.1% (w/v) sorbitol, and 0.015% (w/v) PS 80 at pH 5.5. No preservatives were added.	C0524T05, C0524T06, C0524T11, C0524T08, C0524T09, C0524T13, C0524T23, C0524T24
3'	[redacted]	It is Centocor's intent to launch golimumab in a prefilled syringe (PFS) [redacted] or the same PFS in an autoinjector, both containing the identical liquid formulation of golimumab that was used in the Phase 3 studies.	Long-term Extension Studies

b(4)

b(4)

b(4)

2.5.3 Were various drug products used in clinical studies comparable in terms of PK exposure?

As illustrated in Figure 2.5.3.1, various methods were used to link different drug product formulations during the development process.

A biochemical equivalency study was performed to demonstrate that product made by the two cell lines [redacted] was equivalent. A nonclinical, single SC dose PK comparison study of the material produced by the 2 cell lines [redacted] showed that golimumab produced from the 2 different cell lines had similar PK profiles in cynomologus monkeys (Study P-2002-008). See Product and Pharm/Tox reviews for additional details.

b(4)

The liquid and lyophilized formulations were found to be comparable in a nonclinical pharmacokinetic comparability study (Study P-2005-003). See Pharm/Tox review for additional details.

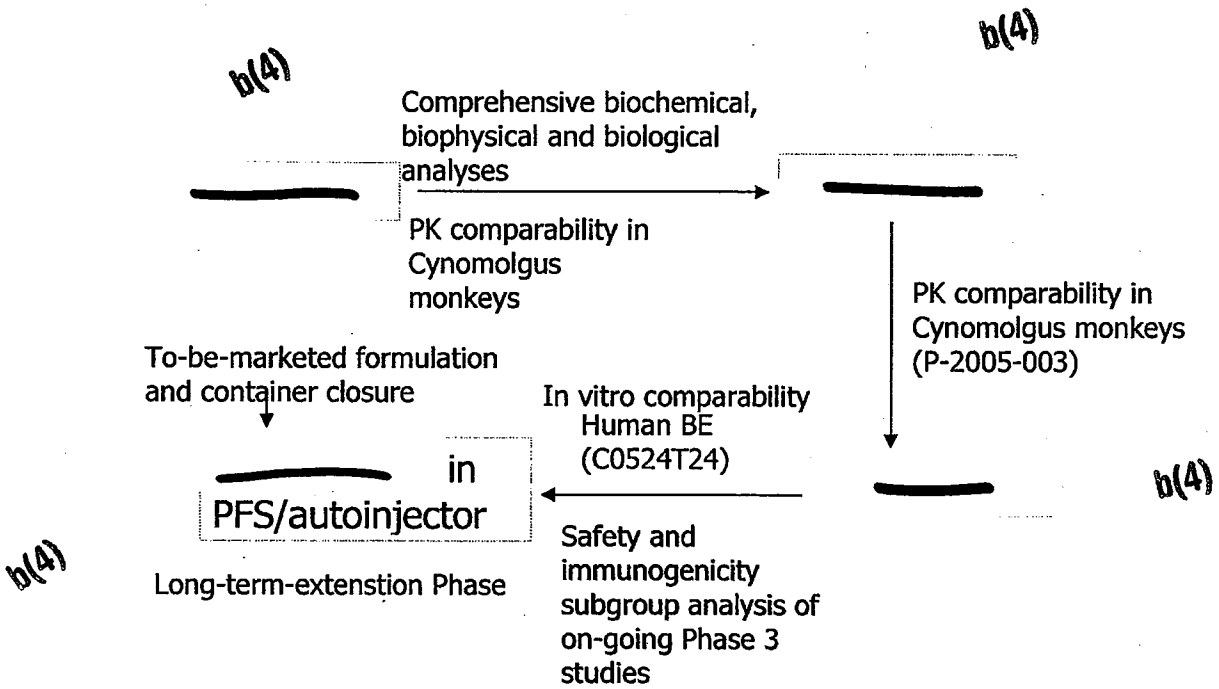


Figure 2.5.3.1. Comparability Studies that Link Various Formulations.

The comparability of the PFS with the Phase 3 LIV presentation and the PFS in the autoinjector presentations were studies with 1) A thorough in vitro comparability assessment of LIV and PFS to compare product quality attributes and stability profiles and 2) A Phase 1 bioequivalence study (Study C0524T24) to assess the PK comparability of the 2 injection methods (ie, 100 mg golimumab single dose administered using an autoinjector versus a needle and syringe) for the delivery of SC golimumab in healthy subjects. The results showed the 90% CI for the ratio of geometric mean AUC(0-49D) values between the 2 injection methods (autoinjector vs. LIV) was 95.17% to 120.55%, which was between the 80% and 125% range; while the 90% CI for Cmax was 96.14% to 127.42%, which fell slightly outside the upper limit of 80% to 125% range. Although the data did not show bioequivalence with Cmax, the difference is small and not considered clinically significant. The Sponsor is proposing a 50 mg dose and in clinical studies, and a 100 mg dose was studied in Phase 3 studies and showed acceptable safety profiles. Therefore, slightly higher Cmax with autoinjector would not pose a safety concern.

In vitro assessment during IND found an increased number of subvisible particles in the PFS. Therefore, a recommendation was made to require clinical data to demonstrate that differences between the presentations will not result in clinically meaningful differences in immunogenicity and safety (PreBLA meeting minutes). The comparison of safety and immunogenicity of autoinjector vs. LIV was analyzed in the on-going Phase 3 studies and the report was reviewed by the Medical Officer. Refer to clinical review for details.

Across study comparison of PK data obtained with various drug product generations showed similar PK parameters.

Ex. 2053-046

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable because golimumab is given via SC injection.

2.6 Analytical

2.6.1 How were the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The bioanalytical methods used to determine the serum golimumab concentrations in the clinical studies were an enzyme-linked immunosorbent assay (ELISA) and 2 electrochemiluminescent immunoassays (ECLIA) (Table 2.6.1.1).

Table 2.6.1.1. Summary of bioanalytical methods and their associated validation reports used to support golimumab clinical studies.

Study	Assays for golimumab		Assays for antibodies to golimumab		PD Assays
	ELISA	ECLIA	Bridging EIA	Neutralizing Ab	
C0466T01	CP2002V-015[a]	N/A	CP2002V-081[d]	NE	NE
C0466T02	N/A	CP2003V-059[b]	CP2002V-081[d]	NE	NE
C0524T01	N/A	CP2003V-059[b]	CP2002V-081[d]	NE	NE
C0524T02	N/A	CP2006V-022[c]	CP2002V-081[d]	CP2005V-055[e]	NE
C0524T03	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	NE
C0524T05	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	484,482,616,617,618,619,30120, 30157, 30272, 30607, 30608, 30452, 30624
C0524T06	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	484,482,616,617,618,619,30120, 30157, 30272, 30607, 30608, 30452, 30624
C0524T08	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	484,482,616,617,618,619,30120, 30157, 30272, 30607, 30608, 30452, 30624
C0524T09	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	484,482,616,617,618,619,30120, 30157, 30272, 30607, 30608, 30452, 30624
C0524T11	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	484,482,616,617,618,619
C0524T13	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	NE
C0524T23	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	NE
C0524T24	N/A	CP2006V-022[c]	CP2002V-081[d]	NE	NE

[a] Validation Report CP2002V-015 has two amendments: CP2002V-015-A2; CP2002V-015-A3
[b] Validation Report CP2003V-059 has one amendment: CP2003V-059-A1
[c] Validation Report CP2006V-022 has four amendments: CP2006V-022-A1, CP2006V-022-A2, CP2006V-022-A3, and CP2006V-022-A4
[d] Validation Report CP2002V-081 has one amendment: CP2002V-081-A1.
[e] Technical Report CP2006T-049
NE = not evaluated in study
NA = not used for this study

Method 1: A validated "sandwich" ELISA method was initially used to determine concentrations of golimumab in human serum (refer to Validation Report CP2002V-015). As shown in Figure 2.6.1.1,

[redacted]

b(4)

Color development correlated with golimumab concentrations.

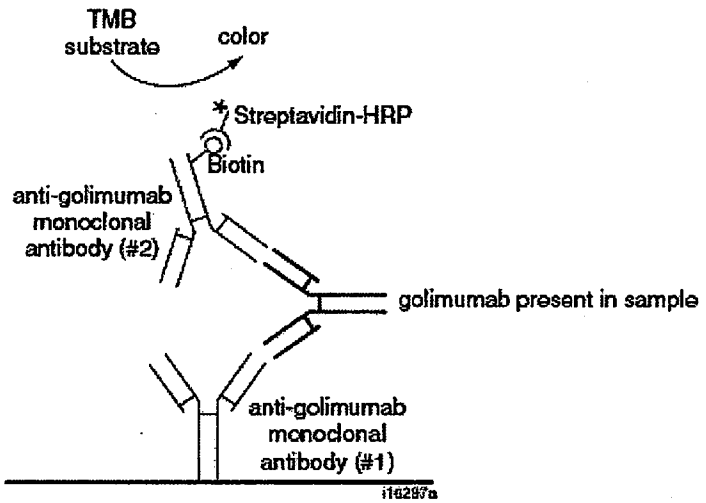


Figure 2.6.1.1. Schematic of ELISA for the Determination of Golimumab Concentrations.

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Table 2.6.1.2. ELISA validation parameters for golimumab in human serum.

Validation Report	CP2002V-015
Assay Type	ELISA
Reference Standard Lot Number	4841-32
Calibration Curve Fit	4-Parameter
Standard Curve Range	7.81 ng/mL to 250 ng/mL
Standard Curve Accuracy and Precision	Accuracy Range: 93.98% to 107.76% Precision Range: 1.15% to 11.27%
Minimum Required Dilution (MRD)	10-fold in buffer (supplemented with 20% goat serum)
Lower Limit of Quantification (LLOQ)	7.81 ng/mL (78.10 ng/mL at the MRD)
Quality Controls Accuracy and Precision	Controls: 25, 75, 135, 150, and 200 ng/mL Inter-assay accuracy: 91.88% to 105.70%, Inter-assay precision: 8.51% to 19.31%,
Dilutional Linearity	2000-fold in assay buffer (supplemented with 20% goat serum)
Specificity	Demonstrated with 2 IgG1 antibodies that do not bind TNFα, 1 IgG1 that does bind to TNFα.
Selectivity	Evaluated in healthy individual serum.

Method 2: A validated competition ECLIA was later used to determine concentrations of golimumab in human serum (refer to Validation Report CP2003V-059). The competition ECLIA utilized technology from [redacted] A master mixture containing biotinylated mAb specific for golimumab, streptavidin-coated magnetic beads, and ruthenium-labeled golimumab was added to the wells. Any golimumab present in the serum sample competed with the ruthenium-labeled golimumab for binding to the biotinylated capture antibody (Figure 2.6.1.2). b(4)

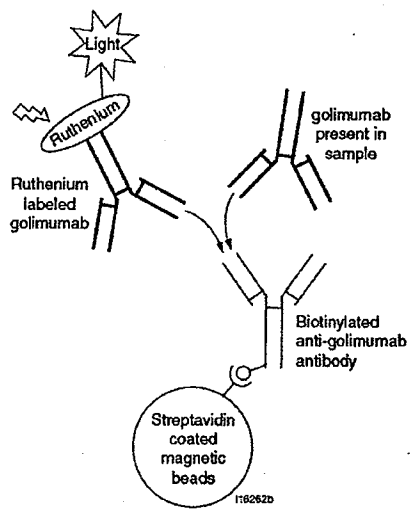

Figure 2.6.1.2. Schematic of Competition ECLIA for the Determination of Golimumab Concentrations.

Table 2.6.1.3. Competition ECLIA validation parameters for golimumab in human serum.

Validation Reports:	CP2003V-059
Assay Type	Competition ECLIA
Reference Standard Lot Number	4841-32
Calibration Curve Fit	4-parameter
Standard Curve Range	300 to 50,000 ng/mL
Standard Curve Accuracy and Precision	Accuracy: 91.03% to 101.59% Precision: 2.62% to 6.76%
Lower Limit of Quantification (LLOQ)	300 ng/mL at the MRD
Minimum Required Dilution (MRD)	Neat
Quality Control Accuracy and Precision	Controls (analyzed neat): 500; 1,000; 2,000; 5,000; 10,000; 50,000 ng/mL Intra-assay Accuracy: 95.63% to 113.35% Intra-assay Precision: 2.85% to 12.46% Controls (analyzed neat): 300, 400, 500, 1,000 ng/mL Inter-assay Accuracy: 95.10% to 112.18% Inter-assay Precision: 6.08% to 17.17% Controls: 10,000; 50,000 ng/mL after dilution Intra-assay Accuracy: 99.61% to 110.44% Intra-assay Precision: 3.25% to 6.11%%
Dilutional Linearity	10-fold in pooled human serum
Specificity	Demonstrated with 3 IgG1 antibodies, 1 IgG4, and 1 IgG1 that does not bind to TNFα, and 1 IgG1 fusion protein
Selectivity	Demonstrated in pooled and individual normal human and RA patient serum.
Stability	Freeze/thaw: 3 cycles

Method 3: The ECLIA method for determination of golimumab concentrations in human serum was updated from a competition assay to a sandwich format (refer to Validation Report CP2006V-022). This method differed from the competition ECLIA in that the sandwich method utilized 2 anti-golimumab antibodies to bind to golimumab present in samples, forming a "sandwich" (Figure 2.6.1.3).

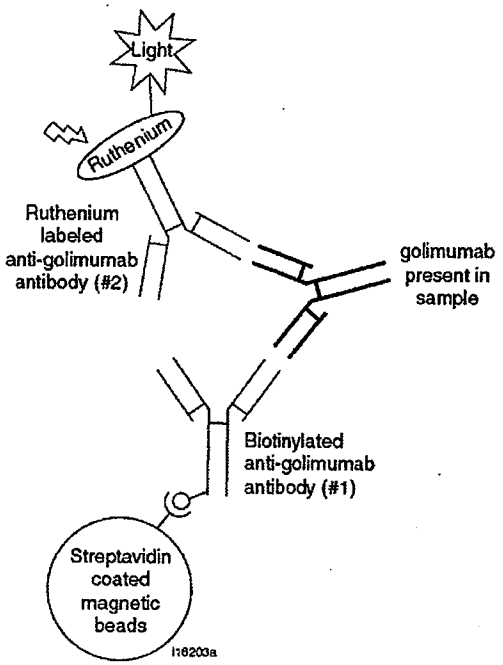

Figure 2.6.1.3. Schematic of Sandwich ECLIA for the Determination of Golimumab Concentrations.

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Table 2.6.1.4. Sandwich ECLIA validation parameters for golimumab in human serum.

Validation Reports:	CP2006V-022; CP-2006V-022-A3*; CP-2006V-022-A4
Assay Type	ECLIA
Reference Standard Lot Number	D05PJ7456
Calibration Curve Fit	4-Parameter
Standard Curve Range	15.63 to 1,000 ng/mL
Standard Curve Accuracy and Precision	% Accuracy: 97.40% to 103.01% % CV (precision): 2.19% to 5.59%
Minimum Required Dilution (MRD)	10-fold dilution in buffer (PBS, 2%BSA, 1% Tween 20)
Lower Limit of Quantification (LLOQ)	20 ng/mL (200 ng/mL at the MRD)
Quality Control Accuracy and Precision	Controls (at MRD): 10, 50, 100 ng/mL Inter-assay Accuracy: 86.33% to 98.73% Inter-assay Precision: 2.90% to 14.53% Intra-assay Accuracy: 98.52% to 109.59% Intra-assay Precision: 4.58% to 13.55% Controls: 10, 50, 100 ng/mL after dilution Inter-assay Accuracy: 103.58% to 106.29% Inter-assay Precision: 1.32% to 8.72% Intra-assay Accuracy: 109.90% to 119.96% Intra-assay Precision: 4.44% to 11.92% Total Error:

Control (ng/mL)	Inter-assay accuracy (% RE)	Inter-assay precision (% CV)	Total Error (% RE ÷ % CV)
750	-4.2 %	7.0%	11.3%
400	-5.5%	10.1%	15.6%
50	1.9%	10.5%	12.4%
20	14.9%	19.9%	34.9%

Dilutional Linearity	10,000-fold in PBS, 2%BSA, 1% Tween 20
Specificity	Demonstrated with 3 IgG1 antibodies, 1 IgG4 antibody, and 1 IgG1 fusion protein that do not bind TNFα
Method Reproducibility	Demonstrated with repeat analysis of incurred samples
Stability	RT: 24 hours, 4 °C: 4 weeks –20 °C: 8 weeks –70 °C: 36 months*
Selectivity	Demonstrated with six individual human serum samples*

BSA = bovine serum albumin
PBS = phosphate-buffered saline
RT = room temperature
* Addendum # 3

Method Cross-Validation:

The three methods were cross-validated when newer methods were introduced to the development program.

ELISA and competition ECLIA: A total of 30 incurred human samples from clinical study C0466T01 analyzed previously by the ELISA method were repeated on 6 occasions with the competition ECLIA to establish method comparability. Six samples with results less than LLOQ using the ELISA method were repeated in the competition ECLIA assay and all results were less than LLOQ on all testing occasions. On the 6 testing occasions, the mean results from the competition ECLIA assay were within ± 40% of the original ELISA result for at least 16 of 23 samples (69.57%). This method independent accuracy based acceptance limit was defined as 40% (20% accuracy for each of the 2 assay occurrences). These data demonstrate that the competition ECLIA method is comparable to the ELISA method.

Competition ECLIA and sandwich ECLIA: The competition and sandwich ECLIA assay methods were compared using 4 controls in human serum ranging between 300 ng/mL and 300,000 ng/mL. Controls tested in the competition ECLIA demonstrated accuracy (% recovery) ranging from 103.41% to 130.65%, with % CV values ranging between 0.54% and 46.04%. The same controls in the sandwich ECLIA method demonstrated accuracy (% recovery) ranging from 85.19% to 114.54%, with % CV values ranging between 0.74% and 15.28%. These data demonstrate that the sandwich ECLIA method is comparable to the competition ECLIA method.

2.6.2 How immunogenicity was determined? What bioanalytical methods were used to detect anti-drug antibodies and those that were neutralizing antibodies in serum or other biological fluids?

An enzyme immunoassay (EIA) method was developed to detect antibodies to golimumab in human serum samples (Validation Reports CP2002V-081 and CP2002V-081-A1). The EIA followed a bridging format in which detection occurred when anti-golimumab antibodies cross-linked solid phase and labeled solution phase golimumab molecules (Figure 2.6.2.1).

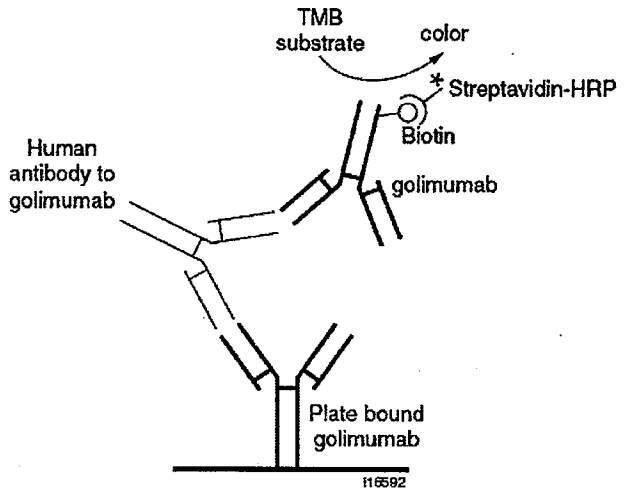

Figure 2.6.2.1. EIA Schematic for Determination of Antibodies to Golimumab.

Table 2.6.2.1. EIA validation parameters for antibodies to golimumab in human serum.

Validation Report	CP2002V-081-A1
Assay Type	EIA
Controls	• Negative Control: pooled normal human serum • Positive Controls: – 50 ng/mL affinity purified cynomologus antibody to golimumab – Pool of 8 human sera – 42 individual human sera – One murine mAb
Cut-off[a]	> 0.143 OD units
MRD	10-fold in PBS with 1%BSA
Recovery	• Mean recovery of 84.18% for positive monkey control at 0.6 to 5000.0 ng/mL in human serum • Mean recovery of 89.18% for positive murine control at 0.6 to 5000.0 ng/mL in human serum
Sensitivity	12 ng/mL for murine positive antibody (1.2 ng/mL times the 10-fold MRD) and 49 ng/mL for monkey positive antibody (4.9 ng/mL times the 10-fold MRD)
Dilutability	Serial 1:2 dilutions of individual human positive sera resulted in a regular decline in OD values
Precision	Intra-assay (intra-run): Mean 2.91% CV positive human serum pool Mean 12.92% CV negative human serum pool Inter-assay (inter-day): Mean 5.68% CV for positive human serum pool Mean 23.64% CV for negative human serum pool
Specificity	Demonstrated • Positive control signals inhibited by golimumab but not by another human IgG1 • Detection of antibodies to golimumab but not antibodies to another IgG1
Interference	Detection of positive antibodies was • Reduced 0% to 32% by 1 ng/mL golimumab • Reduced 3% to 66% by 10 ng/mL golimumab • Reduced 73% to 97% by 100 ng/mL golimumab • Not detected at 1000 ng/mL or greater golimumab
Robustness	Robustness was demonstrated for the range of incubation times specified in the method
Stability	Freeze /Thaw: 4 cycles (positive human serum pool) –20°C: 62 days (positive human serum pool) –70°C: 47 months (individual positive human sera)

BSA = bovine serum albumin
PBS = phosphate-buffered saline
[a] Cut-off was determined in the initial validation, refer to Validation Report CP2002V-081

Immunoassay formats to measure golimumab concentrations can be affected by the presence of antibodies to golimumab. The data showed that the presence of antibodies to golimumab may result in lower measured concentrations for golimumab, thereby reducing the accuracy and apparent level of detection of golimumab, specifically at golimumab concentrations below 10

μg/mL. The interference of antibodies to golimumab on the competition ECLIA and ELISA formats was not evaluated.

A 3-tiered system was used to assess antibodies to golimumab by EIA. First, subject serum samples were screened at the MRD and results exceeding the cut-off were presumed positive. Second, the presumed positive samples were confirmed to be positive by competitive inhibition with 50 μg/mL golimumab. Third, 1:2 serial dilutions of positive sera were analyzed, and the titer was defined as the greatest dilution that produced an assay result greater than the cut-off.

Due to golimumab interference in this EIA, results of clinical samples were classified into 1 of 3 categories:

- Positive: a sample confirmed to contain antibodies to golimumab, regardless of the presence or absence of golimumab in the sample
- Negative: a sample with neither detectable antibodies to golimumab nor detectable golimumab.
- Undetectable (or inconclusive): a sample without detectable antibodies to golimumab, but containing detectable levels of golimumab (ie, indicating possible interference by the presence of golimumab in the serum).

Neutralizing Assay:
Serum samples from clinical studies identified as containing antibodies to golimumab were further characterized for the ability of those antibodies to neutralize the bioactivity of golimumab using a cell-based assay (Table 2.6.1.1). The NAb cell-based bioassay was used to determine the presence of anti-golimumab neutralizing antibodies in human serum or plasma matrix for samples identified as immune response positive by EIA. In this assay method, WEHI cell death (the reporter system for the assay) occurs in the presence of free TNFα. Golimumab neutralizes free TNFα, and was in turn neutralized by anti-golimumab neutralizing antibodies. Therefore, in the presence of anti-golimumab neutralizing antibodies TNFα remained unbound in the sample and induced WEHI cell death in a concentration dependent manner (Figure 2.6.2.2).

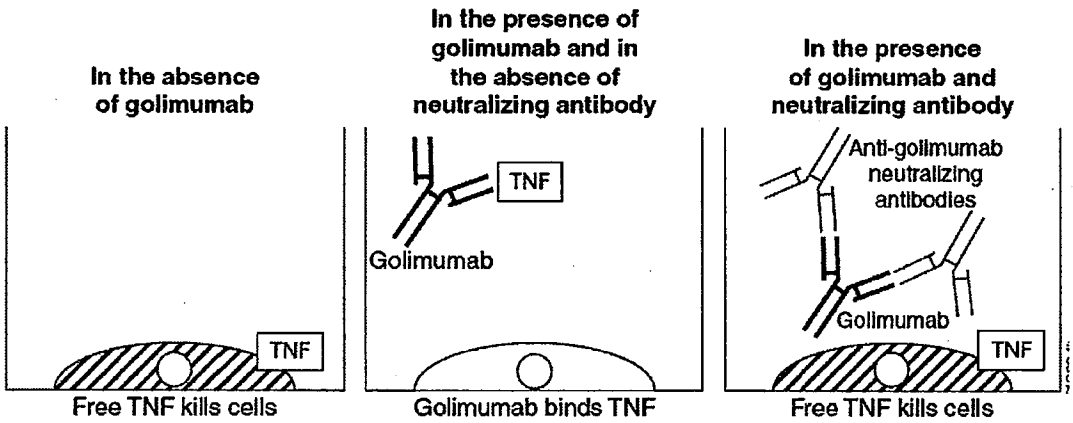

Figure 2.6.2.2. Schematic of the Cell-Based NAb Assay

Table 2.6.2.2. Anti-golimumab NAb assay validation parameters for human serum.

Analysis Method	Cell-based bioassay
Validation Report	CP2005V-055
Controls	Assay controls to monitor the baseline of the assay Consistency controls to monitor the ability of the assay to detect NAbs Sample specific controls to monitor any interference from the sample matrix
MRD	20-fold in RPMI media
Assay Cut-off	≥ 13% inhibition change from baseline result is positive[a]
Sensitivity	150 ng/mL of neutralizing anti-golimumab antibody in sample (at the MRD)
Precision	Positive Consistency Controls: • Intra-assay % CV ranged from 1.56% to 4.61% • Inter-assay % CV ranged from 6.64% to 14.60% • Interoperator % CV ranged from 0.71% to 3.63% • Variability between 5 different passage numbers (4, 6, 8, 14, and 17) of WEHI-C527 for the consistency controls ranged from 3.00% to 6.34% CV
Specificity	• Reactivity of unrelated antibodies directed against other known anti-cytokine antibodies was below the minimum detection limit • The minimum concentration of exogenous golimumab which totally abolished the neutralization capacity of a high affinity antibody was 1.43 µg/mL
Robustness	Robustness was demonstrated for the range of incubation times specified for in the method
Stability	Diluted Positive Consistency Controls: • 4 °C: 18 hours Positive Consistency Controls: • Freeze/thaw: 3 cycles • 4 °C: 28 days • –70 °C: 28 days
[a] Refer to Technical Report CP-2006T-049	

Refer to Appendix 4.4 for CMC consult review for assessment of bioanalytical and antibody detection assays.

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39 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 9

4.2 Individual Study Reviews

4.2.1 Study C0466T01: A Phase I, Double-blind, Placebo-controlled, Randomized, Single Ascending Dose, Safety, Pharmacokinetic/Pharmacodynamic Study of the Human Monoclonal Antibody to Human TNFα rTNV148B (CNTO 148) in Patients with Rheumatoid Arthritis

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Study Period:	October 30, 2001 to October 1, 2002
Principle Investigators:	Site 001: Roy Fleischman, MD; Radiant Research; Dallas, TX, USA Site 002: Sanford Roth, MD; Arizona Research and Education; Phoenix, AZ, USA

Objectives: The primary objectives of the study were to assess the short-term safety and pharmacokinetics (PK) of single ascending intravenous (IV) administrations of CNTO 148 in subjects with rheumatoid arthritis (RA). The secondary objectives of the study were to assess the immunogenicity, pharmacodynamics (PD), effects on immune function, and clinical response of single ascending IV administrations of CNTO 148 in subjects with RA.

Design: This was a randomized, double-blind, placebo-controlled study in which adult subjects with active RA received a single IV infusion (infused over a period of 2 hours) of the study agent (CNTO 148 or placebo). Subjects were then followed for PK, PD, efficacy, safety, immune function, and antibody response to CNTO 148 for 16 weeks.

Investigational Product: 0.1, 0.3, 1, 3, 6, or 10 mg/kg IV CNTO 148; Lot number D01PD7065.

Sample Collection for PK: Pre-infusion, end of infusion, 1, 4, 8, 24 hour post-infusion, Day 3, 7, Week 2, 4, 8, 12, 16 post-infusion.

Sample Analysis: Serum concentrations for golimumab (CNTO 148) based on a validated enzyme-linked immunosorbent assay (ELISA) method (Centocor Validation Report CP2002V-015) with a limit of quantification (LOQ) of 0.078 μg/mL at a 1:10 dilution and 1.09 μg/mL at a 1:40 dilution. A 1:10 dilution was used to measure samples from Group I (0.1 and 0.3 mg/kg), and a 1:40 dilution was used to measure samples from Groups II (1 and 3 mg/kg) and III (6 and 10 mg/kg).

Subjects: A total of 57 subjects were screened for inclusion in the study, and 36 were enrolled. Subjects (n = 36) participating in this study had active RA (by American College of Rheumatology [ACR] criteria) for ≥ 3 months from onset of persistent synovitis. Subjects in the study were allowed to be on a stable therapeutic regimen of up to 2 DMARDs, corticosteroids (≤ 10 mg/day prednisone or equivalent), and/or nonsteroidal anti-inflammatory drugs (NSAIDs), for the treatment of their arthritis.

Twenty of the 36 subjects in the study were enrolled at Site 001, and 16 at Site 002. Twenty-six subjects were randomly assigned to receive CNTO 148, and 10 to receive placebo. Among subjects randomly assigned to receive CNTO 148, 3 were assigned to receive 0.1 mg/kg, 3 to receive 0.3 mg/kg, 5 to receive 1 mg/kg, 5 to receive 3 mg/kg, 5 to receive 6 mg/kg, and 5 to receive 10 mg/kg. Of the enrolled subjects, 33 (92%) completed the study.

Across the groups, the subjects were mainly female and Caucasian. The median age of the subjects was 53 years, and the median weight was 72.7 kg. Approximately 64 % of subjects were taking at least 1 concomitant DMARD at study entry.

Results:

Pharmacokinetics:

Three subjects were excluded from the PK analyses. Subject 001004 (1 mg/kg CNTO 148) was excluded because of a PK extrapolation ratio between AUC (0 - last) and AUC of more than 25%, and Subjects 001013 (6 mg/kg CNTO 148) and 002014 (10 mg/kg CNTO 148) each had only 4 of 13 PK samples available for analysis.

Mean serum CNTO 148 concentrations generally peaked between the end of the infusion and 1 hour following the end of the infusion. Detectable concentrations of CNTO 148 were no longer observed by weeks 8, 16, 8, and 12 in the 0.1, 0.3, 1, and 3 mg/kg dose cohorts, respectively. Detectable concentrations of CNTO 148 were still observed in 1 of 5 subjects in the 6 mg/kg dose cohort and in 2 of 5 subjects in the 10 mg/kg dose cohort at the end of the study (Week 16).

The median t1/2 ranged from 6.56 to 19.25 days after a single IV administration at doses ranging from 0.1 mg/kg to 10 mg/kg (Table 1). The t1/2 appeared to be shorter in subjects who received the lower doses (0.1 mg/kg to 1 mg/kg) compared with subjects who received the higher doses (3 mg/kg to 10 mg/kg). The terminal portion of the serum concentration-time curve was not sufficient to fully characterize the t1/2 in the lower-dose cohorts.

The mean CL, Vz, and MRT after IV administration of CNTO 148 ranged from 5 mL/day/kg to 7 mL/day/kg, 58 mL/kg to 126 mL/kg, and 10 days to 24 days, respectively (Table 1). CL and Vz were independent of dose, suggesting linear PK.

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Table 1. Summary of pharmacokinetic parameters; treated subjects.

	CNTO 148 (rTNV148B)					
	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg
Subjects treated	3	3	5	5	5	5
Cmax (μg/mL)						
n	3	3	4	5	4	4
Mean ± SD	2.60 ± 0.33	12.31 ± 3.08	27.69 ± 4.51	70.77 ± 18.92	166.75 ± 42.14	224.80 ± 39.09
Median	2.43	13.95	28.69	69.85	159.68	207.08
Range	(2.40, 2.98)	(8.76, 14.23)	(21.75, 31.64)	(54.10, 101.63)	(124.56, 223.08)	(201.75, 283.30)
tmax (day)						
n	3	3	4	5	4	4
Mean ± SD	0.10 ± 0.02	0.10 ± 0.03	0.08 ± 0.01	0.16 ± 0.15	0.10 ± 0.02	0.09 ± 0.00
Median	0.08	0.08	0.08	0.08	0.10	0.09
Range	(0.08, 0.13)	(0.08, 0.14)	(0.08, 0.09)	(0.08, 0.42)	(0.08, 0.13)	(0.08, 0.09)
AUC (0-14) (μg • day/mL)						
n	3	3	4	5	4	4
Mean ± SD	11.08 ± 1.74	41.73 ± 10.68	142.66 ± 24.22	337.73 ± 104.78	765.56 ± 353.81	1111.2 ± 457.27
Median	10.71	35.87	136.63	317.70	675.41	1089.0
Range	(9.55, 12.98)	(35.27, 54.06)	(120.40, 176.98)	(238.79, 515.47)	(460.36, 1251.1)	(577.49, 1689.1)

	CNTO 148 (rTNV148B)					
	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg
AUC (day • μg/mL)						
n	3	3	4	5	4	4
Mean ± SD	15.15 ± 2.17	65.58 ± 18.81	195.63 ± 53.95	524.21 ± 178.93	1343.6 ± 659.11	2222.4 ± 1490.8
Median	15.78	72.09	177.75	468.38	1198.1	1968.4
Range	(12.73, 16.92)	(44.38, 80.26)	(153.27, 273.75)	(332.76, 813.64)	(769.95, 2208.4)	(700.50, 4252.1)
t1/2 (day)						
n	3	3	4	5	4	4
Mean ± SD	8.45 ± 4.82	11.53 ± 7.35	7.71 ± 1.93	12.71 ± 3.82	16.07 ± 4.02	19.93 ± 13.27
Median	6.56	7.33	8.58	11.20	14.48	19.25
Range	(4.87, 13.93)	(7.25, 20.03)	(4.83, 8.84)	(8.85, 18.33)	(13.37, 21.95)	(5.07, 36.15)
CL (mL/day/kg)						
n	3	3	4	5	4	4
Mean ± SD	6.56 ± 1.09	4.89 ± 1.66	5.39 ± 1.25	6.24 ± 1.92	5.32 ± 2.36	6.72 ± 5.21
Median	6.04	4.19	5.70	6.45	5.38	5.14
Range	(5.82, 7.81)	(3.70, 6.78)	(3.66, 6.49)	(3.71, 9.02)	(2.72, 7.80)	(2.35, 14.25)

	CNTO 148 (rTNV148B)					
	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg
Vz (mL/kg)						
n	3	3	4	5	4	4
Mean ± SD	77.10 ± 38.38	77.01 ± 41.27	58.30 ± 15.13	112.19 ± 39.90	121.12 ± 50.14	126.17 ± 22.29
Median	55.04	70.92	55.57	115.05	129.71	121.60
Range	(54.85, 121.42)	(39.12, 120.99)	(45.22, 76.85)	(59.99, 170.54)	(52.40, 172.65)	(104.23, 157.23)
MRT (day)						
n	3	3	4	5	4	4
Mean ± SD	11.08 ± 4.78	14.84 ± 7.81	10.40 ± 2.80	14.49 ± 2.73	18.89 ± 3.91	23.70 ± 12.77
Median	9.47	12.48	10.74	14.20	17.22	24.28
Range	(7.30, 16.46)	(8.49, 23.56)	(6.70, 13.42)	(11.34, 17.65)	(16.41, 24.71)	(7.53, 38.73)

Figure 1 shows the relationship between Cmax and CNTO 148 dose over the range of 0.1 mg/kg to 10 mg/kg. Ten-fold increases in dose (0.1 mg/kg to 1 mg/kg or 1 mg/kg to 10 mg/kg) resulted in approximately 8- to 11-fold increases in mean Cmax.

Figure 2 shows the relationship between AUC and CNTO 148 dose over the range of 0.1 mg/kg to 10 mg/kg. Ten-fold increases in dose (0.1 mg/kg to 1 mg/kg, 0.3 mg/kg to 3 mg/kg, or 1 mg/kg to 10 mg/kg) resulted in an approximately 8- to 13-fold increases in the mean CNTO 148 AUC.

The mean Cmax and AUC of CNTO 148 appeared to increase in a dose-proportional manner, albeit with large variability. Same linear relationship was demonstrated from 0.1 to 3 mg/kg that covers the proposed dose of 50 mg (Figure 3).

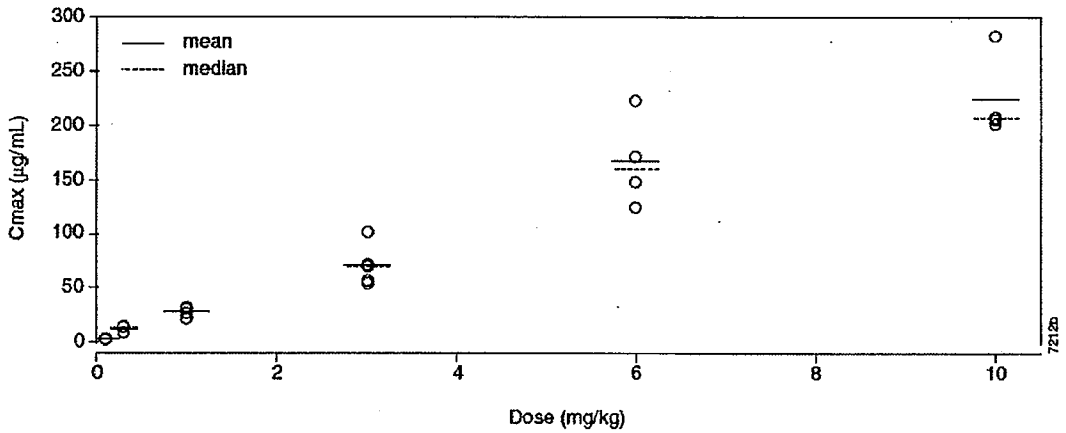


Figure 1. Individual Cmax values (micrograms/mL) with mean and median by dose cohort; treated subjects.

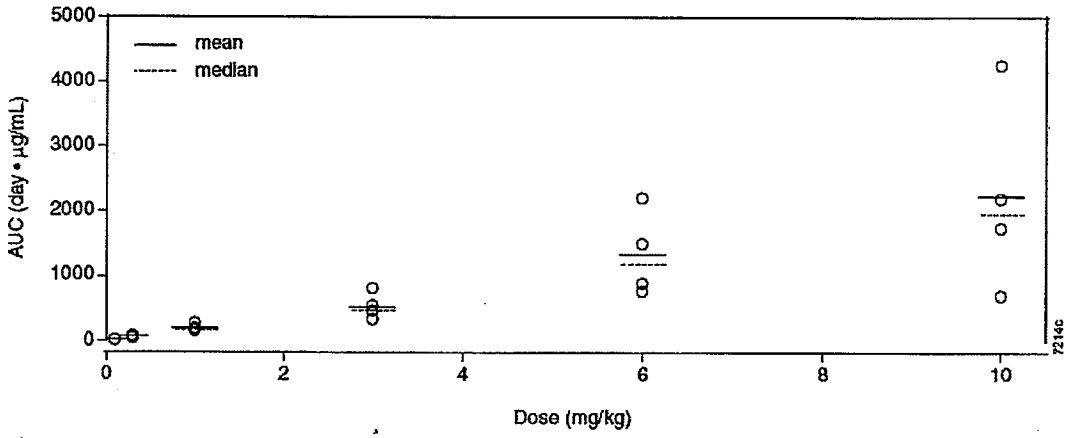
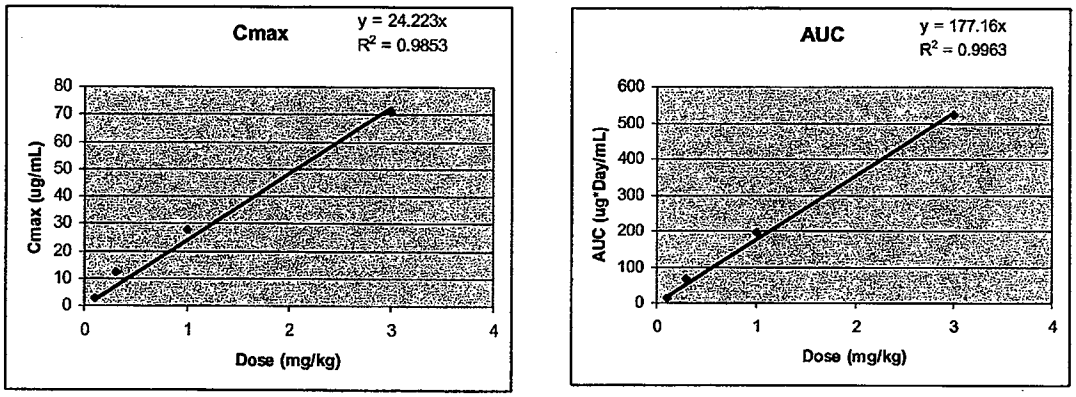


Figure 2. Individual AUC values (day·micrograms/mL) with mean and median by dose cohort; treated subjects.



a) Cmax b) AUC

Figure 3. Relationship between Dose (0.1 to 3 mg/kg) and Cmax (a) and AUC (b).

Conclusions: Single IV doses (up to 10 mg/kg) of golimumab showed acceptable safety profiles in RA patients. Pharmacokinetics over the 0.1 mg/kg to 10 mg/kg dose were dose proportional and cover the proposed dose of 50 mg. The t1/2 of CNTO 148 was between 6.56 and 19.25 days following IV infusion in RA patients.

4.2.2 Study C0466T02: A Phase I, Double-blind, Placebo-controlled Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamics of Single and Multiple Subcutaneous Administrations of the Human Monoclonal Antibody to Human TNFα (CNTO 148) in Patients with Rheumatoid Arthritis

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Study Period: Mar 13, 2002 to Jun 11, 2004
Principle Investigator: James O Posever, MD; University of Arizona; Tucson, AZ, USA

Objectives: Primary objectives were to assess the short-term safety and pharmacokinetic (PK) of single and repeat subcutaneous (SC) administrations of CNTO 148 in subjects with rheumatoid arthritis (RA). Secondary objectives were to assess the immunogenicity, pharmacodynamics (PD), and clinical response of single and repeat SC administrations of CNTO 148 in subjects with RA.

Design: This was a randomized, double-blind, placebo-controlled study. In Stage I, subjects were randomized to receive a single dose of placebo or CNTO 148 at a dose of 0.3 mg/kg, 0.6 mg/kg, 1.0 mg/kg, or 3.0 mg/kg. Subjects were then followed for PK, PD, efficacy, safety, and antibody response to CNTO 148 (immunogenicity) for 16 weeks. The decision to proceed with Stage II was based on a comprehensive safety assessment of Stage I 14 days after the last study agent administration in Stage I. In Stage II, subjects were randomized to receive 3 SC administrations of placebo or CNTO 148 (2-week interval) at a dose of 0.3 mg/kg or 1.0 mg/kg, and followed for PK, PD, efficacy, safety, and antibody response to CNTO 148 through the dosing period and for 16 weeks after the last study agent administration.

Investigational Product: 0.3 mg/kg, 0.6 mg/kg, 1.0 mg/kg, or 3.0 mg/kg SC CNTO 148; Lot numbers D01PD7065ZC, D01PD7065ZD, D01PD7065ZG, D01PD7065ZI, D01PD7065ZJ, and D01PD7065ZL

Sample Collection for PK: Stage I: Pre-dose, 0.5, 1, 2, 4, 8, 24, Day 3, 7, Week 2, 4, 8, 12, and 16 post-injection; Stage II: Pre-dose, 1, 8, 24 hr, Day 3, 7, 17, 21, 31, 35, Week 6, 8, 12, 16 and 20 post-injection.

Sample Analysis: Serum concentrations for golimumab (CNTO 148) were analyzed based on a validated electrochemiluminescence-based (ECLIA) assay (Centocor Validation Report CP2003V-059) with a lower limit of quantification (LLOQ) of 0.30 μg/mL using neat (undiluted) samples.

Subjects: A total of 53 subjects were enrolled at 5 study sites (Stage I: 29 subjects; Stage II: 24 subjects). In Stage I, 9, 5, 5, 5, and 5 subjects received placebo or 0.3 mg/kg, 0.6 mg/kg, 1.0 mg/kg, or 3.0 mg/kg CNTO 148, respectively. Most (96.6%) subjects were Caucasian and the majority (89.7%) were female. The median age of the subjects was 60.0 years.

In Stage II, 9, 7, and 8 subjects received 3 SC administrations of placebo, 0.3 mg/kg CNTO 148, or 1.0 mg/kg CNTO 148, respectively, at 14-day intervals. Most (87.5%) subjects were Caucasian and the majority (87.5%) were female. The median age of the subjects was 54.0 years.

The subjects participating in this study had active RA (by ACR criteria) for ≥ 3 months from onset of persistent synovitis. Subjects were allowed to be on a stable therapeutic regimen of up to 2 DMARDs, corticosteroids (prednisone ≤ 10 mg/day or equivalent), and/or NSAIDs, for the treatment of their arthritis.

Results:

Pharmacokinetics:

PK analysis demonstrated that CNTO 148 was slowly absorbed into the systemic circulation with a median time corresponding to Cmax (Tmax) occurring approximately 2 days to 5 days after a single SC administration at doses ranging from 0.3 mg/kg to 3.0 mg/kg. It was slowly eliminated from the circulation with a median terminal half-life (t1/2) ranging approximately between 14 days to 20 days.

The extent of CNTO 148 exposure (maximum observed serum concentration of CNTO 148 [Cmax] and AUC) appeared to increase with the dose after a single SC administration at 0.3 mg/kg, 0.6 mg/kg, and 3.0 mg/kg. No clear separation was observed in systemic exposure between 0.6 mg/kg and 1.0 mg/kg after a single SC administration (Figure 1). The total body clearance as a function of systemic bioavailability (CL/F), t1/2, and mean residence time (MRT) appeared to be dose-independent at 0.3 mg/kg, 0.6 mg/kg, and 3.0 mg/kg (Table 1 and Figure 2).

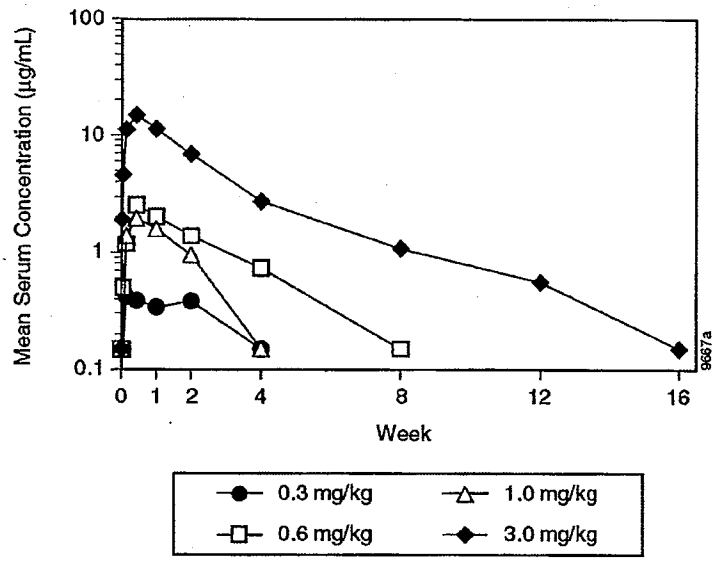
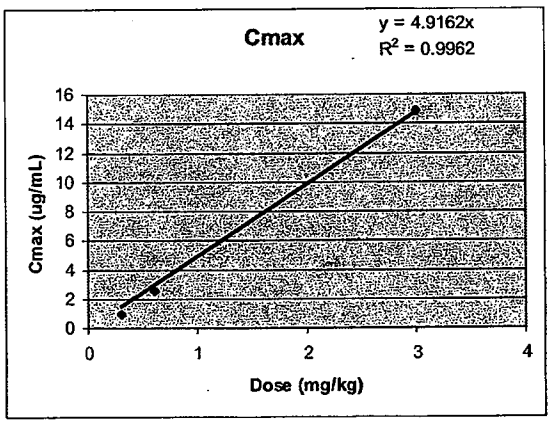


Figure 1. Mean serum CNTO 148 concentrations over time by dose; Stage I CNTO 148 treated subjects.

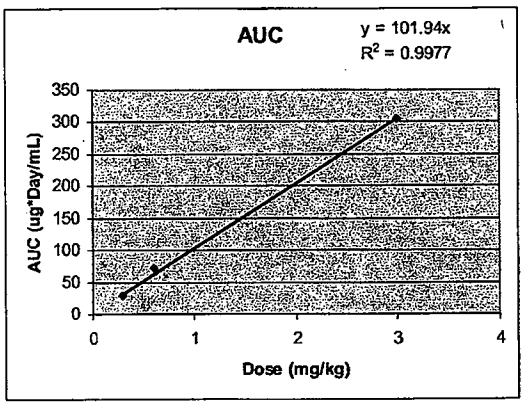
Table 1. Summary of derived pharmacokinetic parameters; treated subjects in Stage I (single administration).

	CNTO 148			
	0.3 mg/kg	0.6 mg/kg	1.0 mg/kg	3.0 mg/kg
Subjects treated	5	5	5	5
Cmax (μg/mL)				
n	2	5	5	5
Mean ± SD	0.96 ± 0.18	2.55 ± 2.07	2.03 ± 1.03	14.88 ± 8.71
Median	0.96	2.16	1.70	14.14
Range	(0.83, 1.09)	(0.49, 5.96)	(1.37, 3.84)	(4.66, 25.13)
tmax (days)				
n	2	5	5	5
Mean ± SD	5.04 ± 2.89	4.06 ± 2.21	3.05 ± 2.46	3.26 ± 2.17
Median	5.04	3.09	2.99	2.06
Range	(3.00, 7.08)	(3.03, 8.02)	(1.00, 7.06)	(2.01, 7.04)
AUC (0-t) (μg • day/mL)				
n	2	5	5	5
Mean ± SD	10.85 ± 1.71	25.40 ± 17.55	21.03 ± 8.15	147.15 ± 74.28
Median	10.85	25.59	18.06	168.91
Range	(9.64, 12.06)	(5.61, 52.89)	(14.59, 35.21)	(54.80, 226.57)
AUC (μg • day/mL)				
n	1	4	5	5
Mean ± SD	29.10 ± NA	71.20 ± 47.79	65.34 ± 60.21	303.95 ± 155.69
Median	29.10	59.20	37.56	330.12
Range	(29.10, 29.10)	(29.83, 136.58)	(29.36, 171.65)	(127.54, 511.77)
t1/2 (days)				
n	1	4	5	5
Mean ± SD	16.79 ± NA	14.90 ± 5.68	45.67 ± 63.34	24.16 ± 12.70
Median	16.79	15.34	13.83	19.97
Range	(16.79, 16.79)	(8.90, 20.01)	(12.20, 158.15)	(8.18, 40.85)
CL/F (mL/day/kg)				
n	1	4	5	5
Mean ± SD	10.11 ± NA	11.63 ± 6.96	22.09 ± 11.57	12.71 ± 7.39
Median	10.11	11.03	26.79	9.09
Range	(10.11, 10.11)	(4.40, 20.07)	(5.79, 33.94)	(5.86, 23.57)

	CNTO 148			
	0.3 mg/kg	0.6 mg/kg	1.0 mg/kg	3.0 mg/kg
Vz/F (mL/kg)				
n	1	4	5	5
Mean ± SD	244.79 ± NA	213.98 ± 84.49	736.69 ± 335.15	408.22 ± 333.57
Median	244.79	203.96	648.42	275.25
Range	(244.79, 244.79)	(123.60, 324.39)	(515.94, 1321.8)	(222.09, 1003.6)
MRT (days)				
n	1	4	5	5
Mean ± SD	24.80 ± NA	22.99 ± 8.29	58.39 ± 71.59	29.01 ± 15.18
Median	24.80	23.46	21.27	23.17
Range	(24.80, 24.80)	(13.97, 31.06)	(19.61, 184.83)	(14.06, 53.31)



a) Cmax



b) AUC

Figure 2. Relationship between Dose (0.3 to 3 mg/kg, excluding 1 mg/kg) and Cmax (a) and AUC (b).

The extent of CNTO 148 exposure also appeared to be dose-dependent over the doses ranging from 0.3 mg/kg to 1.0 mg/kg after 3 biweekly SC administrations of study agent (Table 2 and Figure 3).

Table 2. Summary of derived pharmacokinetic parameters; treated subjects in Stage II (multiple administrations).

	CNTO 148	
	0.3 mg/kg q2w	1.0 mg/kg q2w
Subjects treated	6	8
Cmax (first) (μg/mL)		
n	6	8
Mean ± SD	1.10 ± 0.75	4.81 ± 3.81
Median	1.43	3.47
Range	(0.00, 1.88)	(1.75, 13.81)
Cmax (third) (μg/mL)		
n	5	7
Mean ± SD	1.18 ± 0.51	8.05 ± 2.11
Median	1.37	7.05
Range	(0.47, 1.78)	(5.82, 11.47)
tmax (days)[a]		
n	5	8
Mean ± SD	3.89 ± 1.79	3.91 ± 2.41
Median	3.12	3.00
Range	(2.95, 7.09)	(1.05, 8.22)
AUC (0-t) (μg • day/mL)		
n	6	8
Mean ± SD	10.41 ± 6.24	43.06 ± 26.74
Median	12.28	36.23
Range	(2.14, 17.43)	(18.79, 106.08)
AUC (μg • day/mL)		
n	4	7
Mean ± SD	60.17 ± 10.09	288.83 ± 99.08
Median	62.74	238.25
Range	(45.90, 69.30)	(194.89, 475.52)
t1/2 (days)		
n	5	8
Mean ± SD	18.02 ± 9.71	29.18 ± 24.35
Median	15.16	17.63
Range	(10.23, 34.41)	(8.22, 75.13)

[a] tmax is the time corresponding to Cmax (first).

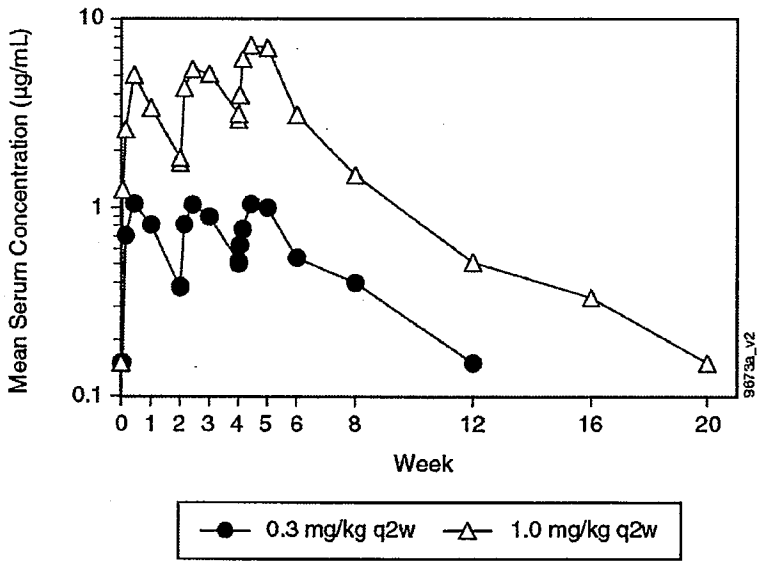


Figure 3. Mean serum CNTO 148 concentrations over time by dose; Stage II CNTO 148 treated subjects.

Relative Bioavailability (Cross-study Comparison): Based on a cross-study comparison of mean AUC_{inf} data at dose levels of 0.3 mg/kg and 3.0 mg/kg from studies C0466T02 (SC) and C0466T01 (IV), the absolute bioavailability of golimumab after a SC administration was estimated to be 44% and 58%, respectively. The data from the single-dose 1.0 mg/kg cohort were not included for bioavailability estimation since this cohort was deemed to be an outlier. The ratio of mean dose-normalized AUCinf (SC vs IV) was 53%.

Mean Dose-Normalized AUC, SC	Mean Dose-Normalized AUC, IV	Ratio (SC/IV)
105 µg*day/mL	198 µg*day/mL	53%

4.2.3. Study C0524T13: A Study to Evaluate the Pharmacokinetics of a Single Subcutaneous Administration of 1 mL of 100 mg/mL Liquid Formulation of Golimumab to Healthy Male Subjects

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Study Period: Jan 24, 2006 to May 2, 2006
Principle Investigator: Stuart Harris, M.D., Ph.D.
Study Site: PRA International, 9755 Ridge Drive, Lenexa, KS 66219

Objectives: To evaluate the pharmacokinetics (PK) profile and PK variability of golimumab following a single subcutaneous (SC) injection of 1 mL of 100 mg/mL golimumab as a liquid formulation administered to healthy subjects and to evaluate the safety and tolerability of a single SC injection of the liquid formulation of golimumab in healthy subjects.

Investigational Product: Golimumab for SC injection was supplied in 2 mL single use glass vials as a sterile liquid. Each vial contained 1 mL of 100 mg/mL golimumab. The study agent was from Lot Number D05PJ7456.

Sample Collection: Blood samples for PK analyses were collected at the following time points: approximately within 1 hour prior to study agent dosing, 12 hours after study agent dosing, and at study days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 22, 29, 36, 43, 50, 57, 64, and 71 days.

Sample Analysis: Serum golimumab concentrations were measured using a validated electrochemiluminescent immunoassay (ECLIA) method.

Subjects: A total of 30 subjects who met pre-specified inclusion criteria were enrolled and all received 100 mg of golimumab. Twenty-eight subjects completed the study. Two subjects discontinued the study during the outpatient period. One subject was lost to follow-up and did not return to the clinic after discharge from the Study Unit on Day 15. The second subject who tested positive for cocaine was discontinued from the study on Day 22 for using an unacceptable concomitant medication.

Subjects: A total of 30 subjects who met pre-specified inclusion criteria were enrolled and all received 100 mg of golimumab. Two subjects discontinued the study during the outpatient period. All subjects were males. 70.0% (21/30) were Caucasian. The mean age was 32.9 years (range: 19 to 44 years). The mean BMI was 25.52 kg/m^2.

Results:
Pharmacokinetic Results:
Of the 30 randomized subjects, complete PK profiles were collected for 28 subjects. However, Cmax was still estimable from the available concentration data for the 2 subjects who prematurely terminated from study participation. After a single 100 mg SC dose, golimumab attained a mean peak serum level (Cmax) of 5.38 μg/mL, at the median tmax of 3.5 days. The extent of golimumab exposure as presented by mean AUClast and mean AUCinf values were

83.03 and 84.35 day*µg/mL, respectively. Golimumab exhibited a slow and an apparently monophasic elimination from serum (Figure 1) with a median t1/2 of 11.0 days and a mean apparent clearance (CL/F) of about 1.35 L/day. The CV% on all PK parameters ranged from 32% to 56%.

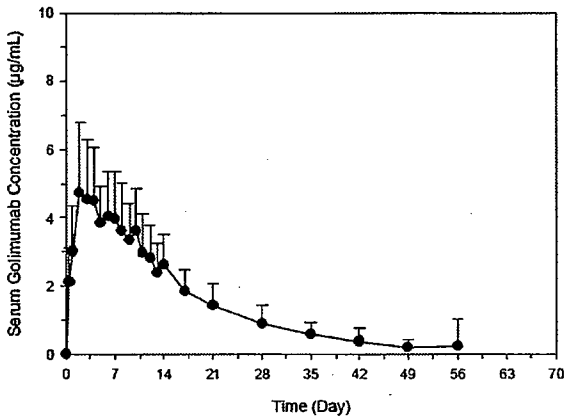

Figure 1. Mean (SD) Golimumab Serum Concentrations over Time After a Single SC Dose of 100 mg Golimumab to Healthy Male Subjects.

Table 1. Pharmacokinetic Parameters.

Parameter	Summary Statistics		
	N	Mean ± SD	CV%
Cmax (ug/mL)	30	5.38 ± 1.92	35.72
AUC (0-49D) (day*µg/mL)	28	80.48 ± 25.77	32.02
AUC (0-70D) (day*µg/mL)	28	83.93 ± 27.39	32.63
AUClast (day*µg/mL)	28	83.03 ± 27.68	33.33
AUCinf (day*µg/mL)	24	84.35 ± 30.57	36.24
Vz/F (mL)	24	20,964.98 ± 7,720.44	36.83
CL/F (mL/day)	24	1,348.52 ± 514.19	38.13
	N	Median (min – max)	CV%
tmax (day)	30	3.50 (2.00-10.00)	56.07
t1/2 (day)	24	10.98 (5.35 ± 20.60)	35.42

4.2.4. Study C0524T23: A Study to Assess the Pharmacokinetics and Safety/Tolerability of a Single Subcutaneous Administration of a Liquid Formulation of Golimumab to Healthy Male Caucasian and Japanese Subjects

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Study Period:	Sept 7, 2006 to Feb 22, 2007
Principle Investigator:	Kenneth T. Kim, MD
Study Site:	West Coast Clinical Trials, LLC, 5630 Cerritos Avenue, Cypress, CA 90630

Objectives: To assess the pharmacokinetic (PK) profiles of golimumab following a single subcutaneous (SC) injection of 50 and 100 mg golimumab as a liquid formulation administered to healthy male Caucasian and Japanese subjects.

Investigational Product: Golimumab (supplied in 2 mL single use glass vials). Each vial contained approximately 1 mL of 100 mg/mL golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80. The study agent was from Lot Number D05PJ7456.

Sample Collection: Blood samples for PK analyses were collected at the following time points: approximately within 1 hour prior to study agent dosing, –1 hour pre-study agent dosing (predose, 0 hour) and at 12 (0.5 day), 24 (1 day), 48 (2 days), 72 (3 days), 96 (4 days), 120 (5 days), 144 (6 days), 168 (7 days), 240 (10 days), 336 (14 days), 504 (21 days), 672 (28 days), 840 (35 days), 1008 (42 days), and 1176 (49 days).

Sample Analysis: The analysis of serum samples for the concentrations of golimumab (CNTO 148) was performed by Centocor (Radnor, Pennsylvania) using a quantitative, sandwich electrochemiluminescent immunoassay (ECLIA) technique.

Subjects: Overall there were 51 male subjects who participated in the study and received the assigned dose of study medication. There were 12 subjects in each of the 50 and 100 mg Japanese treatment groups and 14 and 13 subjects in the 50 and 100 mg Caucasian treatment groups, respectively. Among these 51 subjects, 4 Caucasian subjects prematurely discontinued from the study and 3 Caucasian subjects were recruited to compensate for these discontinuations.

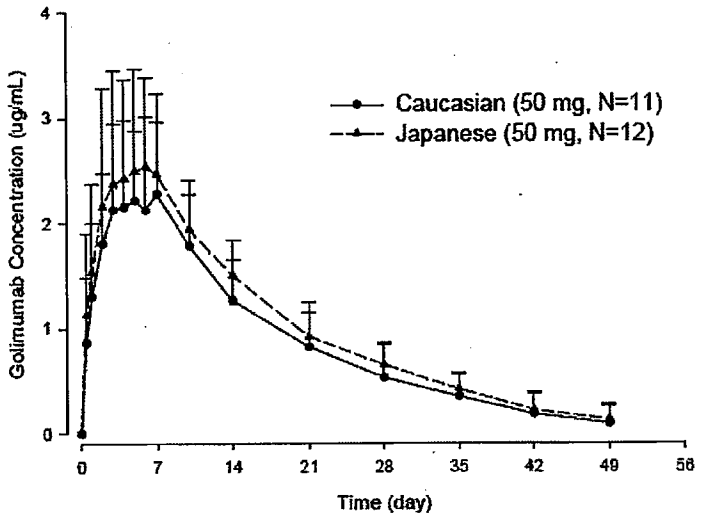
The mean weights for the Caucasian groups (70.3 and 70.9 kg for the 50 and 100 mg groups, respectively) were slightly higher than those for the Japanese groups (65.3 and 65.1 kg for the 50 and 100 mg groups, respectively).

Results:

Pharmacokinetic Results:

PK is comparable between Caucasian and Japanese. The mean AUC(0-∞) values at 50 mg were 47.69 and 53.25 μg*day/mL for Caucasian and Japanese subjects, respectively, with mean Cmax values of 2.48 and 2.82 μg/mL, respectively. The mean t1/2 values were almost identical for the Caucasian and Japanese subjects (11.06 and 11.92 days, respectively). Similar observations were seen for the Caucasian and Japanese subjects administered 100 mg golimumab (Table 1 and

Figure 1). Regardless of race, serum golimumab exposure increased as dose increased from 50 mg to 100 mg. The mean apparent volume of distribution remained constant with dose increase (range: 224.18 to 262.16 mL/kg).



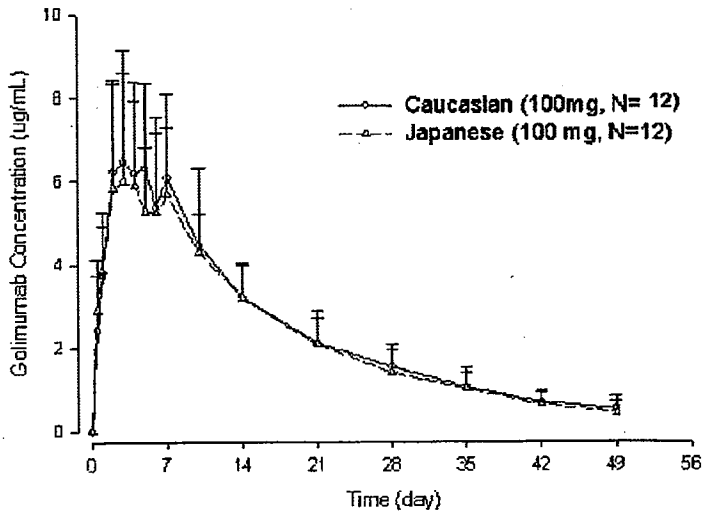
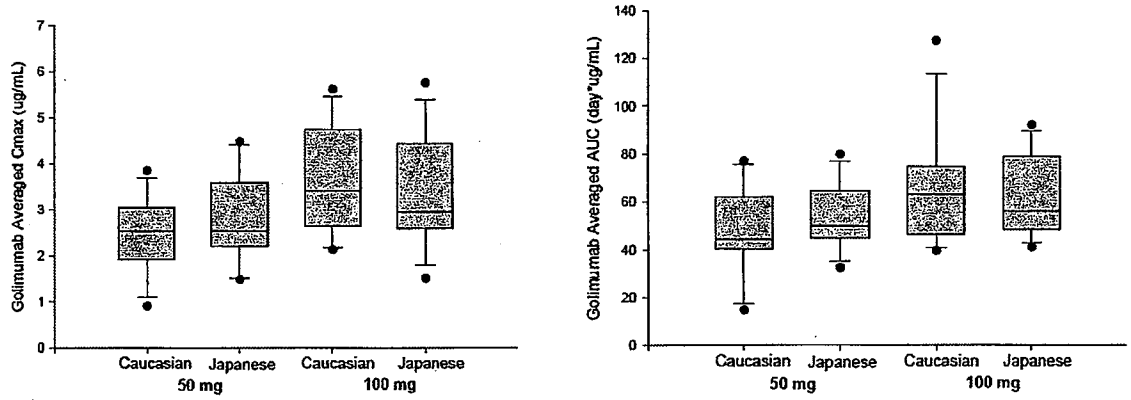


Figure 1. Mean (SD) Serum Concentrations of Golimumab Versus Time for Each Treatment Group (linear scale).

Figure 2 presents comparisons for dose-normalized AUC(0-∞) and Cmax between Japanese and Caucasian subjects for each dose.



Cmax AUC(0-∞)

Figure 2. Dose-Normalized Cmax (Left) and AUC(0-∞) (6B) between Caucasian and Japanese Subjects after Single Subcutaneous Administration at 50 mg and 100 mg.

Table 1. Summary of Mean (± SD) Pharmacokinetic Parameters for Each Treatment Group.

Treatment Group (N)	AUC(0-∞) (µg·day/mL)	AUC(0-49D) (µg·day/mL)	Cmax (µg/mL)	Tmax (day)	t1/2 (day)
50 mg Japanese (12)	53.25 ±13.06	49.64 ±12.17	2.82 ±0.97	5.51 ±1.90	11.92 ±2.32
50 mg Caucasian (10) [a]	47.69 ±17.49	44.49 ±15.04	2.48 ±0.77	4.82 ±1.78	11.06 ±2.69
100 mg Japanese (12)	121.63 ±33.89	112.54 ±29.61	6.72 ±2.35	4.00 ±1.95	12.56 ±2.41
100 mg Caucasian (12)	129.72 ±47.12	118.61 ±39.09	7.21 ±2.31	4.25 ±1.55	13.28 ±2.31

Notes: SD = standard deviation.

[a] N = 11 for Cmax and Tmax.

Conclusion: The disposition of golimumab in Caucasian subjects was comparable to that observed in Japanese subjects after SC administration of golimumab. No apparent differences in PK parameters were observed between Caucasian and Japanese at the same dose level.

4.2.5. Study C0524T24: A Phase 1, Randomized, Open-label, Parallel-design, Inpatient/Outpatient Study to Assess the Bioequivalence of a Single-dose Subcutaneous Administration of Golimumab Delivered by the Centocor Autoinjector or a Needle and Syringe in Healthy Subjects

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Study Period:	Jan 17, 2007 to Jun 26, 2007
Principle Investigator:	Barrie March, MD
Study Site:	PRACS Institute, Ltd., Fargo, ND

Objectives: To assess the bioequivalence of a single 100 mg SC injection of golimumab, supplied as 1.0 mL sterile liquid, delivered by 1 of 2 drug injection methods, the Centocor autoinjector or a needle and syringe.

Study: During the primary bioequivalence component of the study, subjects received a single injection of golimumab delivered to the abdomen by either the autoinjector or a needle and syringe. Blood samples for measurement of golimumab concentrations were collected on Days 1 through 8 and on Days 15, 22, 29, 36, 43, 50, and 71.

Investigational Products: For the bioequivalence component, a single 100 mg dose containing 1 mL of golimumab was delivered by SC injection to the abdomen using either the autoinjector or a needle and syringe. Liquid golimumab from the same batch of final drug product was used to fill both the syringe housed in the autoinjectors and the vials from which the solution was drawn to manually deliver injections via needle and syringe. Golimumab was supplied from lot numbers V06PL9882 (autoinjectors) and 6HS3U (vials for administration with a needle and syringe).

Subjects: Of the 156 subjects randomly assigned to an injection method, 77 were assigned to receive single dose of 100 mg golimumab with the autoinjector and 79 were assigned to receive a single dose of golimumab with a needle and syringe; all randomized subjects received 1 dose of golimumab. All study subjects were male. The majority of subjects, 67 (84.8%) in the needle and syringe group and 69 (89.6%) in the autoinjector group, were Caucasian. The median age in both groups was 25 years (ranges were 18 to 50 and 18 to 49 years, respectively). Overall, demographic characteristics at baseline were well balanced between the groups.

Results:
A total of 141 subjects (71 subjects in the needle and syringe group and 70 subjects in the autoinjector group) met the criteria to be included in the evaluable PK population. Overall reasons for exclusion were incomplete injection due to wet injection (n = 8; 4 subjects in each injection method group), incomplete PK profile (n = 5; 3 subjects in the needle and syringe group and 2 in the autoinjector group) and positive status for antibodies to golimumab (n = 2; 1 subject in each injection method group).

The sponsor conducted additional 2 sensitive analysis. The first sensitivity analysis included subjects in the PK evaluable population plus subjects who had an incomplete injection due to a

wet injection. The second sensitivity analysis included subjects in the PK evaluable population plus subjects who had an incomplete PK profile due to missing PK collections but had sufficient serum concentration data to assess Cmax and tmax.

PK Results:
Following a single SC administration of 100 mg golimumab, mean Cmax values were 5.97 and 6.63 mg/mL for the needle and syringe group and the autoinjector group, respectively (Table 1). For both groups, Cmax values showed marked interindividual variability with percent coefficient of variation (%CV) values of approximately 50%. The median tmax values (ie, 6 days for needle and syringe, 5 days for autoinjector) were also similar between the 2 injection method groups. In addition to having similar PK absorption parameters (Cmax, tmax), golimumab also exhibited similar disposition parameters (t1/2, CL/F) following a single administration of golimumab between the 2 injection method groups. Median t1/2 values were 11.7 and 11.2 days, and mean CL/F (body-weight adjusted) were 15.13 and 14.59 mL/day/kg for the needle and syringe group and the autoinjector group, respectively.

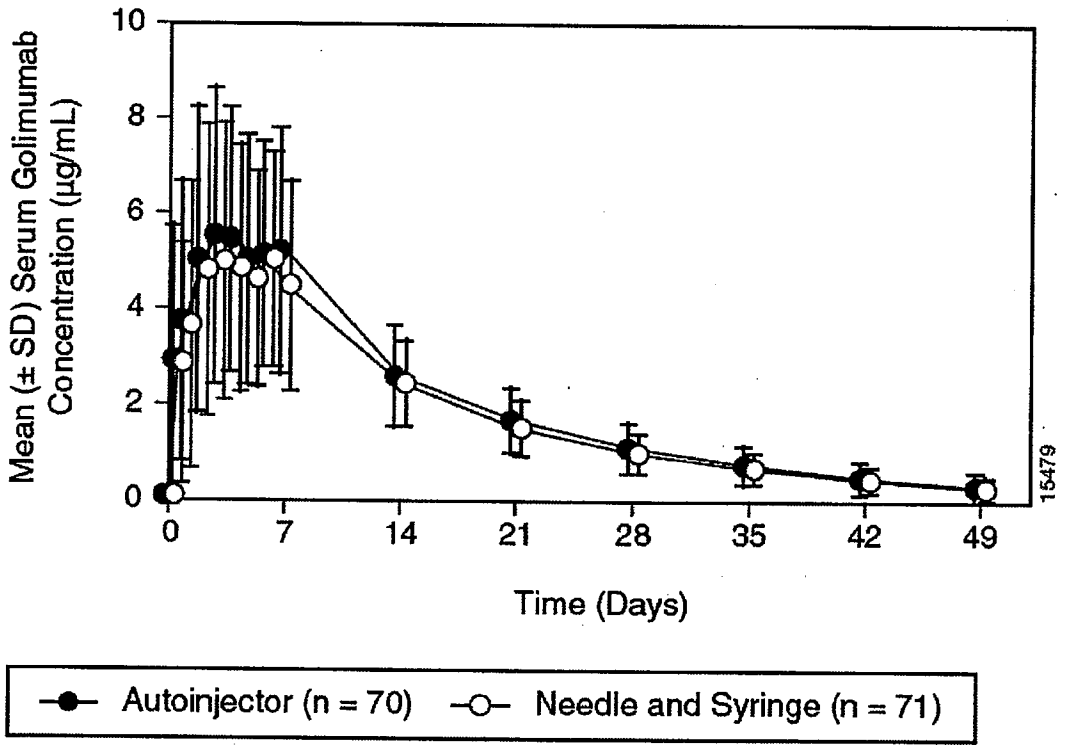


Figure 1. Mean (SD) serum golimumab concentration (micrograms/mL); Evaluable PK population.

Table 1. Summary of golimumab pharmacokinetic parameter estimates; evaluable PK population.

	Golimumab SC 100 mg	
	Needle and Syringe	Autoinjector
Subjects evaluable	71	70
Cmax (μg/mL)		
n	71	70
Mean ± SD	5.97 ± 3.014	6.63 ± 3.320
Median	5.53	5.68
IQ range	(3.61, 7.47)	(4.36, 8.78)
Range	(1.8, 13.6)	(1.8, 15.4)
AUC(0-49 D) (μg.day/mL)		
n	71	70
Mean ± SD	88.88 ± 36.847	97.39 ± 43.163
Median	80.64	88.57
IQ range	(62.92, 111.81)	(64.74, 116.07)
Range	(28.2, 189.9)	(32.1, 242.9)
AUClast (μg.day/mL)		
n	70	70
Mean ± SD	87.13 ± 36.372	96.72 ± 43.663
Median	79.62	88.58
IQ range	(61.71, 111.38)	(64.16, 116.07)
Range	(26.0, 189.9)	(29.6, 242.9)
AUCinf (μg.day/mL)		
n	70	70
Mean ± SD	95.72 ± 39.287	104.25 ± 47.910
Median	91.64	94.56
IQ range	(69.74, 118.57)	(69.15, 125.78)
Range	(31.0, 200.1)	(33.9, 277.6)
tmax (day)		
n	71	70
Mean ± SD	4.73 ± 1.820	4.66 ± 1.702
Median	6.00	5.00
IQ range	(3.00, 6.00)	(3.00, 6.00)
Range	(1.0, 7.0)	(1.0, 7.0)
λz (L/day)		
n	71	70
Mean ± SD	0.06 ± 0.016	0.06 ± 0.015
Median	0.06	0.06

	Golimumab SC 100 mg	
	Needle and Syringe	Autoinjector
IQ range	(0.05, 0.07)	(0.05, 0.07)
Range	(0.0, 0.1)	(0.0, 0.1)
t1/2 (day)		
n	71	70
Mean ± SD	12.02 ± 3.142	11.81 ± 3.059
Median	11.69	11.19
IQ range	(9.84, 13.28)	(9.53, 13.40)
Range	(5.5, 23.9)	(6.5, 20.4)
CL/F (mL/day)		
n	70	70
Mean ± SD	1246.42 ± 566.012	1174.82 ± 558.749
Median	1091.18	1057.62
IQ range	(843.41, 1433.91)	(795.06, 1446.20)
Range	(499.8, 3227.6)	(360.3, 2948.9)
CL/F (mL/day/kg)[a]		
n	70	70
Mean ± SD	15.13 ± 6.715	14.59 ± 6.475
Median	13.57	13.10
IQ range	(10.69, 17.40)	(10.00, 18.17)
Range	(5.9, 36.6)	(5.5, 33.7)
Vz/F (mL)		
n	70	70
Mean ± SD	20967.62 ± 10590.02	19334.89 ± 9350.535
Median	19220.51	17307.80
IQ range	(14461.19, 25501.06)	(12767.77, 23486.76)
Range	(5599.5, 76119.7)	(6150.6, 50788.4)
Vz/F (mL/kg)[a]		
n	70	70
Mean ± SD	253.33 ± 120.978	240.66 ± 111.328
Median	236.70	215.93
IQ range	(168.19, 295.26)	(163.82, 283.90)
Range	(81.2, 864.0)	(92.8, 624.7)

[a] Body weight-adjusted value.

BE analysis:

The with evaluable PK population for bioequivalence shows that the 90% CI for the ratio of geometric means for AUC(0-49D) values between the 2 injection methods was 95.17% to 120.55%; which falls between the 80% to 125% range. The 90% CI for Cmax was 96.14% to 127.42%, which falls slightly outside the stipulated 80% to 125% range (Table 2).

Table 2. Summary of golimumab pharmacokinetic parameter estimates (Cmax and AUC(0-49D)) (primary endpoints); evaluable PK population.

	Golimumab SC 100 mg	
	Needle and Syringe	Autoinjector
Subjects evaluable	71	70
Cmax (μg/mL)		
n	71	70
Mean	5.97	6.63
Geometric mean	5.91	6.54
Ratio of geometric means (%)[a]		110.7
90% CI[b]		(96.14, 127.42)
AUC(0-49D) (μg.day/mL)		
n	71	70
Mean	88.88	97.39
Geometric mean	88.89	95.22
Ratio of geometric means (%)[a]		107.1
90% CI[b]		(95.17, 120.55)

[a] Ratio = geometric mean of the PK parameter for subjects injected with autoinjector / geometric mean of the PK parameter for subjects injected with needle and syringe

[b] Golimumab in the two groups will be considered bioequivalent if the 90% CIs for both Cmax and AUC(0-49D) fall within 80% and 125%.

Three separate analyses (including a prespecified sensitivity analysis, a post-hoc sensitivity analysis and a post-hoc intent-to-treat analysis) demonstrated that the 90% CIs for both Cmax and AUC(0-49D) fell within the 80% to 125% range when the sample size was slightly increased by including subjects with an incomplete injection due to wet injection, and/or subjects with an incomplete PK profile, and/or subjects positive for antibodies to golimumab (data not shown).

Conclusion: The evaluable PK population results indicate that golimumab administered by autoinjector and needle and syringe met the bioequivalence criterion for AUC(0-49D) but slightly exceeded the upper limit of the 90% CI for Cmax. Golimumab exhibited similar PK profiles following a single SC administration when delivered by either the needle and syringe or the autoinjector.

4.3 Pharmacometrics Review

Regulatory Issues

In this BLA submission, a population PK modeling approach was used to obtain estimates of typical PK parameters for golimumab in each of the 3 target disease populations (subjects with RA, PsA or AS), and determine the covariates that may significantly impact the PK parameters.

The aim of this review is to review sponsor's population PK analyses and verify the labeling statements derived based on these analyses.

Sponsor's Analysis

Population PK analysis was performed separately for each of the three disease indications (RA, PsA, and AS) using the available serum concentration data for the Week-24 analysis of 4 Phase 3 studies (C0524T05 and C0524T06 for RA, C0524T08 for PsA, and C0524T09 for AS).

Pooled serum golimumab concentration data from 315 subjects in C0524T05 and 279 subjects in C0524T06 were included in the population PK analysis in the RA population. 337 subjects in C0524T08 and 312 subjects in C0524T09 were analyzed in the population PK analysis for the PsA and AS populations, respectively. The evaluable subjects in the population data sets must have received at least 1 golimumab dose and had at least 1 measurable serum golimumab concentration randomized.

RA:

RA Study Description:

Study C0524T05: A multicenter, randomized, double-blind, placebo-controlled study of SC golimumab with and without MTX in subjects with active RA who have not been previously treated with MTX. Eligible subjects were randomized to 1 of the following 4 treatment groups:

- Group I (n = 160): Placebo SC injections at Week 0 and every 4 weeks thereafter through Week 48; MTX 10 mg/week starting at Week 0 followed by an escalation to 20 mg/week by Week 8 and continuing at 20 mg/week through Week 48.

- Group II (n = 159): Golimumab 100 mg SC injections at Week 0 and every 4 weeks thereafter through Week 48; placebo (sham MTX) capsules through Week 48 with escalation of doses (ie, number of placebo capsules) in a manner similar to the other groups.

- Group III (n = 159): Golimumab 50 mg SC injections at Week 0 and every 4 weeks thereafter through Week 48; MTX 10 mg/week starting at Week 0 followed by an escalation to 20 mg/week by Week 8 and continuing at 20 mg/week through Week 48.

- Group IV (n = 159): Golimumab 100 mg SC injections at Week 0 and every 4 weeks thereafter through Week 48; MTX 10 mg/week starting at Week 0 followed by an escalation to 20 mg/week by Week 8 and continuing at 20 mg/week through Week 48.

Study C0524T06: A multicenter, randomized, double-blind, placebo-controlled study of SC golimumab with and without MTX in subjects with active RA despite MTX therapy. Eligible subjects were randomized to 1 of the following 4 treatment groups (with a possible early-escape regimen change at Week 16):

- Group I (n = 133): Placebo SC injections at Weeks 0, 4, 8, 12, 16, and 20, followed by golimumab 50 mg SC injections at Week 24 and every 4 weeks thereafter through Week 48; a stable dose of MTX.
- Group II (n = 133): Golimumab 100 mg SC injections at Week 0 and every 4 weeks thereafter through Week 48 and placebo (sham MTX) capsules.
- Group III (n = 89): Golimumab 50 mg SC injections at Week 0 and every 4 weeks thereafter through Week 48 and a stable dose of MTX.
- Group IV (n = 89): Golimumab 100 mg SC injections at Week 0 and every 4 weeks thereafter through Week 48 and a stable dose of MTX.

At Week 16, subjects who had < 20% improvement from baseline in both swollen (SJC) and tender (TJC) joint counts entered a double-blind early escape regimen:

- Group I: Golimumab 50 mg SC every 4 weeks through Week 48 and a stable MTX dose.
- Group II: Golimumab 100 mg SC every 4 weeks through Week 48 and a stable MTX dose.
- Group III: Golimumab 100 mg SC every 4 weeks through Week 48 and a stable MTX dose.
- Group IV: Golimumab 100 mg SC every 4 weeks through Week 48 and a stable MTX dose.

PK sampling:

Study No.	Indication	Visit	W0	W4	W8	W12	W14	W16	W20	W24	W28
C0524T05	RA	PK scheme	X	X	X	X		X	X	X	
										X	
C0524T06	RA	PK scheme	X	X	X	X	X	X	X	X	
								X			
								X			

Methods:

Data

The population PK dataset for the RA indication contained a total of 3,411 measurable golimumab concentration values from 594 subjects with active RA (315 subjects from C0524T05 and 279 subjects from C0524T06). Most (81%) of the subjects in the study were female, the majority (80%) were Caucasian, the mean age was 50.4 years, and the overall duration of RA disease was approximately 6 years (range: 0.1 to 49.6 years). Most (84%) subjects were receiving concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and many subjects received concomitant MTX or oral corticosteroids (66% and 56% subjects, respectively).

Model

A one-compartment PK model using first-order absorption and first-order elimination was selected as the structural PK model to describe the serum concentration-versus-time profiles of golimumab following SC injections based on previous Phase 1 and 2 data (Studies C0466T02 and C0524T13, and C0524T02). The typical population PK parameters (CL/F, V/F, Ka) and their inter-subject variability were estimated using the nonlinear mixed-effect modeling approach (NONMEM) (NONMEM version 6, level 1, ICON Development Solutions, Ellicott City, MD).

Pharsight Trial Simulator® (Pharsight Corporation, Mountain View, CA) (Version 2.2) was used for simulation experiments. SAS (SAS Institute Inc., Cary, NC) (Version 9.1) was used for general statistical analysis.

Covariates

The effects of potential covariates on the PK parameters of golimumab were evaluated. The covariates examined included demographic characteristics, baseline hepatic and renal functions, baseline disease activity, selected concomitant medications, selected comorbidities, and antibody-to-golimumab status, etc. The final population PK data set had more covariates than NONMEM could conveniently handle one time, so GAM analysis was not used; and graphical explorations (ie, post hoc ETAs vs. covariates), followed by formal NONMEM estimation, were used for covariate search.

The significant covariates in affecting CL/F and/or V/F of golimumab are also identified in the final covariate model. In general, a given covariate was considered statistically significant if the addition or removal of this covariate to one PK parameter (eg, CL/F) resulted in an objective function value (OFV) change by more than 10.83 points (ie, p-value < 0.001). However, when there was a mechanistic plausibility for a given covariate (ie, positive antibody status on CL/F), this covariate might be retained in the model even though the OFV change was less than 10.83 points.

Results:

Base model for RA:

Table 1. Summary of Golimumab Population PK Parameter Estimates of the Base Model.

Parameters	Population estimate	95% CI[a] of population estimate	BSV[b] (CV%)[c]	95% CI[a] of BSV (CV%)[c]
CL/F (L/day)	1.72	1.64 -1.80	46.6	38.3 - 54.9
V/F (L)	27.0	24.9 - 29.1	52.6	34.7 - 70.6
Ka (day^{-1})	0.697	0.552 - 0.842	67.5	5.3 - 129.6
Correlation for BSV between CL/F and V/F	0.730	-	-	-
Proportional residual variability (CV%)	28.0	26.8 - 29.2	11.8	1.3 - 22.2

[a] 95% CI: 95% confidence interval. The lower and upper limits for 95% CI were calculated asymptotically using the standard errors estimated by the covariance step in NONMEM.
[b] BSV: Between subject variability, calculated as $(\text{variance})^{1/2}*100\%$.
[c] CV%: Coefficient of variation expressed as percent.

Final model for RA:
Using the Empirical Bayesian Estimate (EBE) of the ETAs in the base model, plots were generated to screen for potential covariate relationships. Of all the covariates, antibody-to-golimumab status, body weight, BSA, CRP, and CRCL appeared to have some relationship with EBE ETA for CL/F. Only body weight appeared to be correlated with EBE ETA for V/F. No covariates affected the EBE ETA for Ka. Serum ALB showed a negative linear relationship with EBE ETA for residual variability.

These covariates were further evaluated using step-wise forward and backward selection method using NONMEM.

As a result, concomitant MTX, antibody-to-golimumab status, standardized body weight (i.e., body weight/70 kg), and standardized baseline CRP (i.e., CRP/1.1 mg/dL) were identified as significant covariates on CL/F. Additionally, standardized body weight was a significant covariate on V/F. None of the covariates were significant for Ka or residual variability.

The final covariate model for CL/F can be given by the following equation:

$$CL/F\,(L/day) = 1.91 \times \left(\frac{Body\ Weight}{70}\right)^{0.605} \times \left(\frac{CRP}{1.1}\right)^{0.0746} \times 0.829^{MTX} \times 1.29^{IRP}$$

where MTX is 1 if concomitant MTX was used and 0 otherwise, IRP is 1 if antibodies to golimumab were present and 0 otherwise.

Likewise, the final covariate model for V/F is given by the following equation:

$$V/F\,(L) = 26.7 \times \left(\frac{Body\ Weight}{70}\right)^{0.678}$$

As summarized in Table 2, the typical population value for CL/F was 1.91 L/day (95% CI: 1.80 to 2.03 L/day) and V/F was 26.7 L (95% CI: 24.5 to 28.7 L) in a typical subject with RA weighing 70 kg. Ka was estimated to be 0.668 (day^{-1}). Between-subject variability (BSV) (CV%) on CL/F, V/F, and Ka was 41.7%, 48.9%, and 86.3 %, respectively. Proportional error (CV%) was 27.8% with a BSV (CV%) of 12.4%. Using the typical population values of CL/F and V/F, the t1/2 of golimumab was calculated to be 9.7 days.

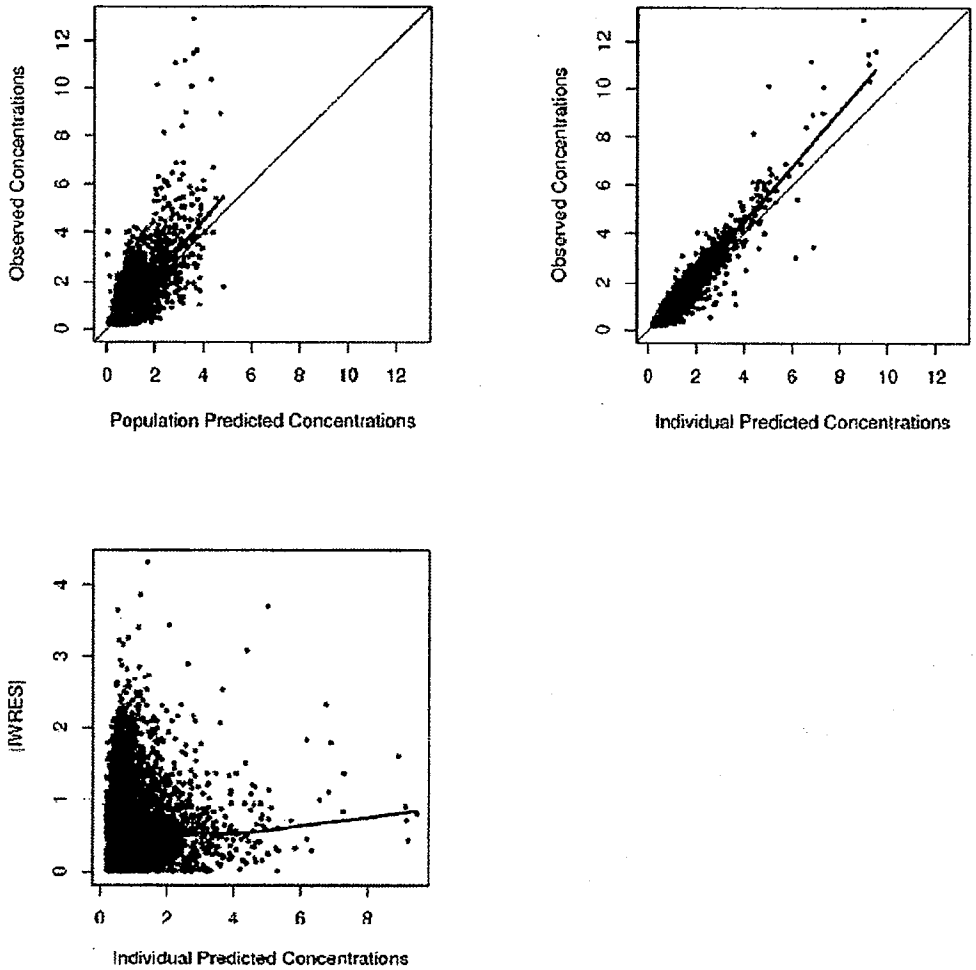
Table 2. Summary of population pharmacokinetic parameters of golimumab and the significant covariates to golimumab PK in subjects with active RA.

Parameters	Population estimate[a]	Median (95% CI)[b] of population estimate	BSV[c] (CV%)[d]	Median [95% CI][b] of BSV (CV%)[d]
CL/F (L/day)	1.91	1.90 (1.80-2.03)	41.7	41.7 (37.4-45.7)
WGT on CL/F[e]	0.605	0.609 (0.447-0.768)	-	-
CRP on CL/F[e]	0.0746	0.0742 (0.0518-0.0965)	-	-
MTX on CL/F[e]	0.829	0.830 (0.785- 0.876)	-	-
IRP on CL/F[e]	1.29	1.29 (1.06- 1.62)	-	-
V/F (L)	26.7	26.5 (24.5-28.7)	48.9	48.6 (38.1-57.1)
WGT on V/F[f]	0.678	0.677 (0.457-0.913)	-	-
Ka (1/day)	0.668	0.686 (0.564- 0.875)	86.3	80.8 (12.9-109.1)
Correlation for BSV between CL/F and V/F	0.716	0.721 (0.593-0.812)	-	-
Proportional residual variability (CV%)	27.8	27.9 (26.7-29.1)	12.4	12.2 (6.3-17.5)

[a]Population estimates by NONMEM with the original final Phase 3 RA population PK dataset from C0524T05 and C0524T06.
[b]Median [95% CI]: median value and 95% confidence interval calculated using 1,000 re-sampled and successfully converged bootstrapping runs. The lower and upper limits for 90% CI were calculated as 2.5th and 97.5th percentiles, respectively, using 1,000 re-sampled and successfully converged bootstrapping runs.
[c]BSV: Between subject variability, calculated as $(\text{variance})^{1/2}*100\%$.
[d]CV%: Coefficient of variation expressed as percent.
[e] $CL/F = 1.91 \times \left(\frac{WGT}{70}\right)^{0.605} \times \left(\frac{CRP}{1.1}\right)^{0.0746} \times 0.829^{MTX} \times 1.29^{IRP}$

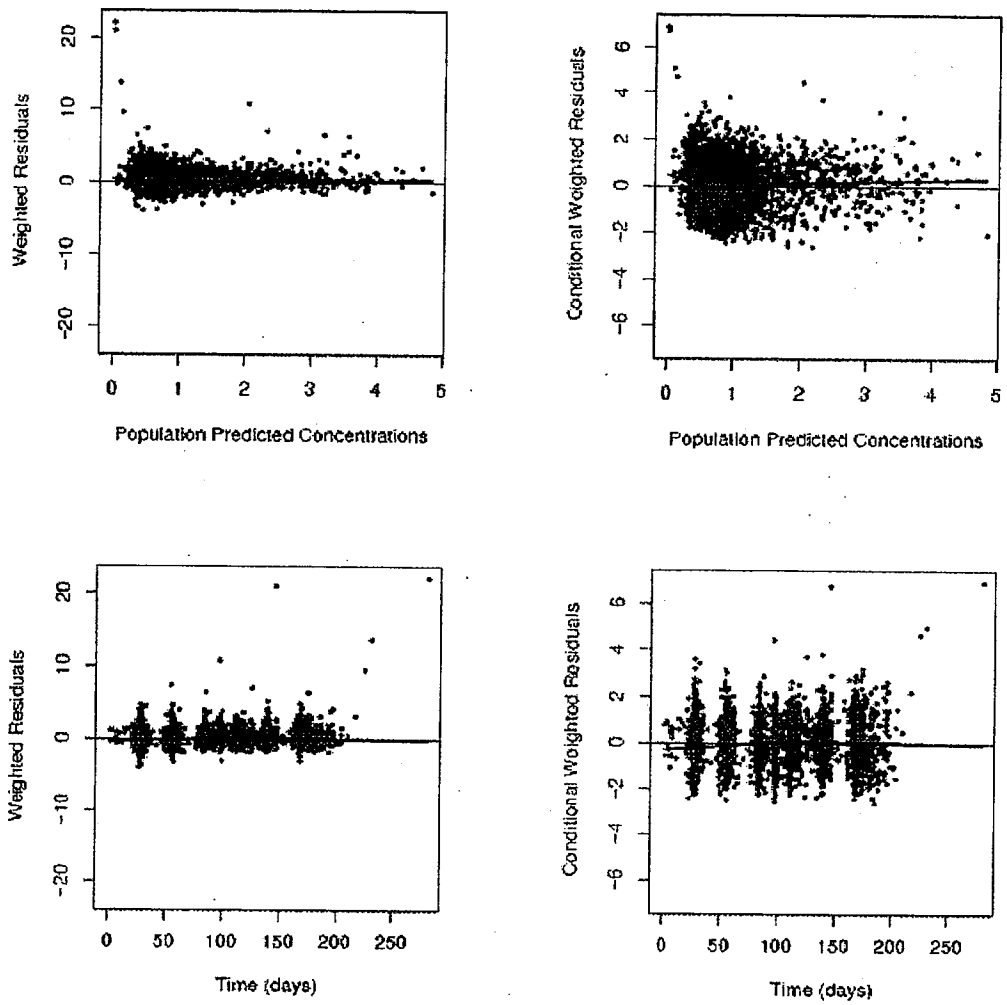
[f] $V/F\ (L) = 26.7 \times \left(\frac{WGT}{70}\right)^{0.678}$

Figure 1 and Figure 2 show goodness of fit (GOF) plots for the final RA PK model. Lines of identity, zero lines, and trend lines are also overlaid as appropriate. In addition, from these GOF plots, some concentrations ≥ 8 µg/mL were underpredicted by the model. However, no serious systematic deviation was identified in the residual plots.



(Figure Note: |IWRES| is absolute individual weighted residuals. Concentrations are in µg/mL.)

Figure 1. General Goodness of Fit for the Final Model (RA).



(Figure Note: Left and right columns are weighted residuals and conditional weighted residuals, respectively. Concentrations are in μg/mL.)

Figure 2. Residual Goodness of Fit for the Final Model (RA).

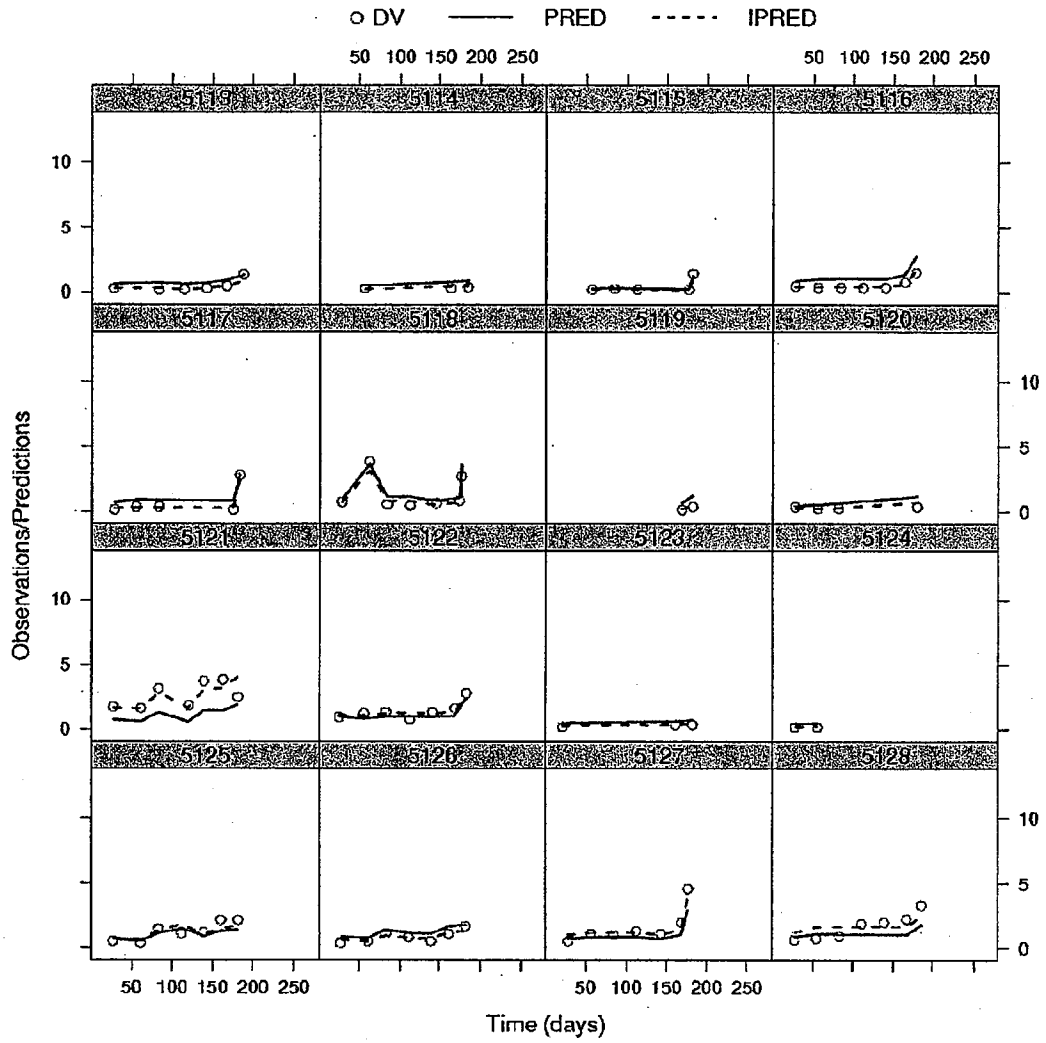


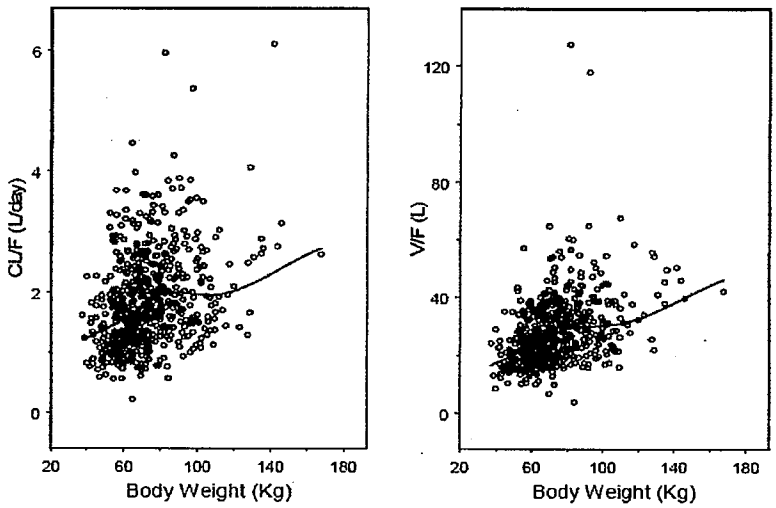
Figure 3. Selected Individual Observed (DV), Model Predicted (PRED), and Individual Predicted (IPRED) Concentration-Time Plots for Subjects in the Population PK Data Set: Final Model (RA). Concentrations are in µg/mL.

This population PK analysis was performed using pooled data from 2 RA subpopulations (ie, active RA subjects naïve to MTX treatment from C0524T05, and active RA subjects despite MTX therapy from C0524T06). For the same dosage regimen, subjects in C0524T05 seemed to have slightly lower serum golimumab concentrations. However, "STDY" (study) was not found to be a significant covariate to CL/F. Therefore, one POP-PK model was used for RA.

Effect of Covariates on Golimumab PK Parameters:

Demographics:
Several demographic characteristics were evaluated as potential covariates including body weight, age, sex, and race. Of these, body weight was the most significant covariate identified for both CL/F and V/F of golimumab. For the 594 subjects with RA in this population PK analysis, the mean body weight was 73.3 kg (range: 37.5 to 167.8 kg). Both CL/F and V/F increased with body weight (Figure 4).

a. Body Weight:



(Figure note Note: LOESS trend lines are overlaid in the plots.)

Figure 4. Empirical Bayesian Estimates of CL/F and V/F Versus Body Weight: Final Model (RA).

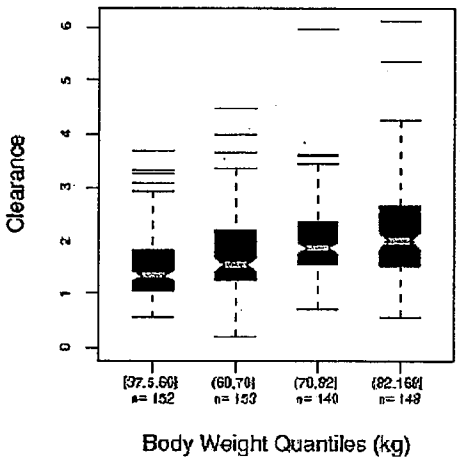


Figure 5. Empirical Bayesian Estimates of CL/F by Body Weight Quartiles: Final Model (RA).

The Monte Carlo simulations showed that, following SC administration of golimumab 50 mg every 4 weeks, median steady-state trough serum golimumab concentration for subjects weighing > 100 kg was 22.2% lower than that for subjects ≤ 100 kg (ie, 0.35 μg/mL versus 0.45 μg/mL, respectively).

b. Age

The effect of age on CL/F and V/F was evaluated in the covariate analysis. For the 594 subjects in the RA data set, the mean age was 50 years (range: 18 to 85 years). Of these 594 subjects, 54 (9%) were more than 65 years of age. Results from the covariate analysis showed that age did not influence either of these 2 PK parameters.

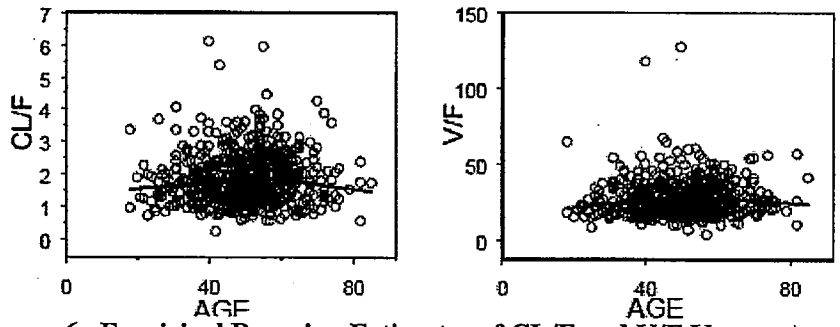
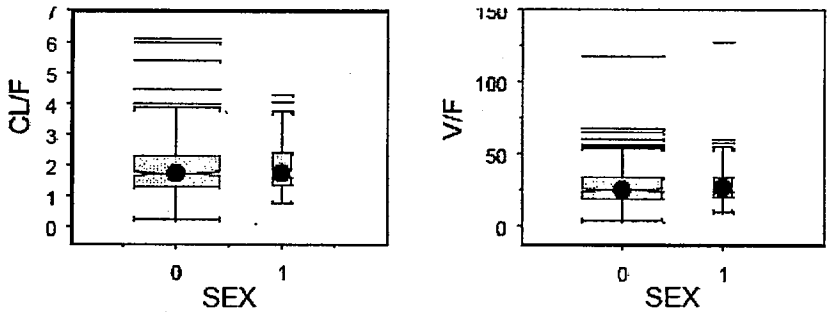


Figure 6. Empirical Bayesian Estimates of CL/F and V/F Versus Age: Final Model (RA).

c. Gender

Sex was evaluated as a potential covariate in this population PK analysis. Of the 594 subjects in the RA data set, 483 (81.3%) were female. Results of the covariate analysis showed that, after body weight adjustment, sex did not significantly influence CL/F or V/F.

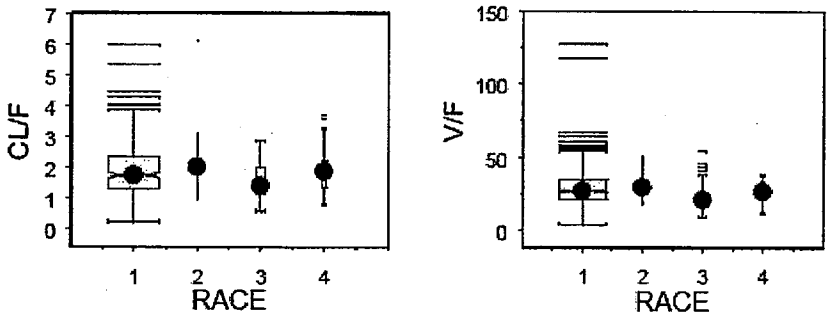


SEX (0=female, 1=male),

Figure 7. Empirical Bayesian Estimates of CL/F and V/F Versus Sex: Final Model (RA).

d. Race

Race was evaluated as a potential covariate on CL/F and V/F. Of the 594 subjects in the RA data set, 474 (79.7%) were Caucasian, 77 (12.9%) were Asian, 5 (0.8%) were Black, and 38 (6.3%) were of other races. Results of the covariate analysis showed there were no significant differences among these race groups in either CL/F or V/F of golimumab.



RACE (1=Caucasian, 2=Black, 3=Asian, 4=Other);

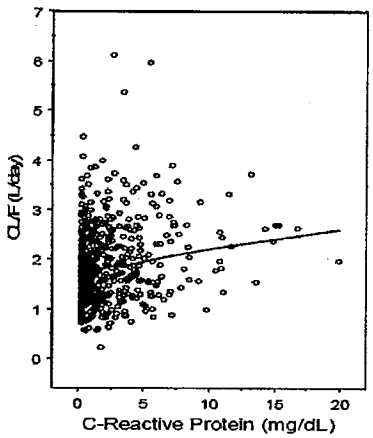
Figure 8. Empirical Bayesian Estimates of CL/F and V/F Versus Race: Final Model (RA).

Baseline disease activities:

Several baseline disease characteristics were assessed as potentially important covariates for golimumab PK. For this RA population analysis, baseline DAS28C, SJC, TJC, CRP, and duration of disease (in years, from the date of initial diagnosis) were each assessed as covariates for CL/F and V/F. Of these baseline measures, CRP was identified as a significant covariate for golimumab CL/F.

For the 594 subjects in the RA data set, the median baseline CRP level was 1.1 mg/dL with an interquartile range of 0.4 to 2.9 mg/dL. As indicated by the small value (0.0746) for the exponent of CRP in the final covariate model for CL/F, however, CRP levels only had a weak correlation with the EBE of CL/F. Therefore, baseline CRP levels would not provide significant predictability for CL/F, and the impact of baseline CRP on steady-state golimumab exposure would not be clinically important.

Figure 9 shows a scatter plot of the EBE of CL/F versus CRP in subjects with RA.



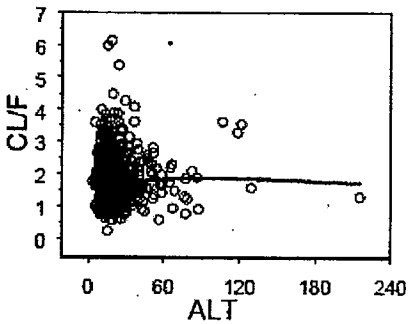
(Figure Note: LOESS trend line is overlaid in the plot.)

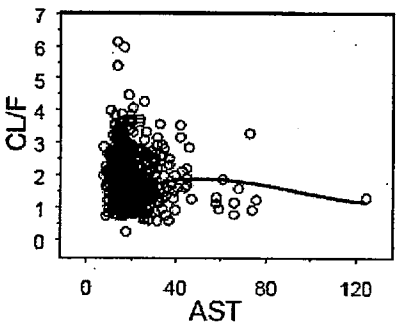
Figure 9. Empirical Bayesian Estimates of CL/F Versus C-Reactive Protein: Final Model (RA).

Hepatic or Renal Functions:
For this population PK analysis, baseline ALT, AST, and serum ALB were used as indicators of hepatic function and baseline CRCL was used as an indicator of renal function.

The majority of subjects had normal hepatic function (ie, overall baseline values of ALT, AST, and ALB were generally within normal ranges). For example, the mean ± SD for ALT, AST, and ALB were 23.0 ± 16.9 U/L, 21.1 ± 10.0 U/L, and 4.2 ± 0.4 g/dL, respectively. Likewise the majority of subjects had normal renal function. That is, the estimated mean baseline CRCL was 108.5 mL/min (range: 32.2 to 278.4 mL/min) for the 594 subjects in the RA data set.

In all, the covariate analysis indicated that baseline ALT, AST, ALB, and CRCL had no significant effects on either CL/F or V/F of golimumab.





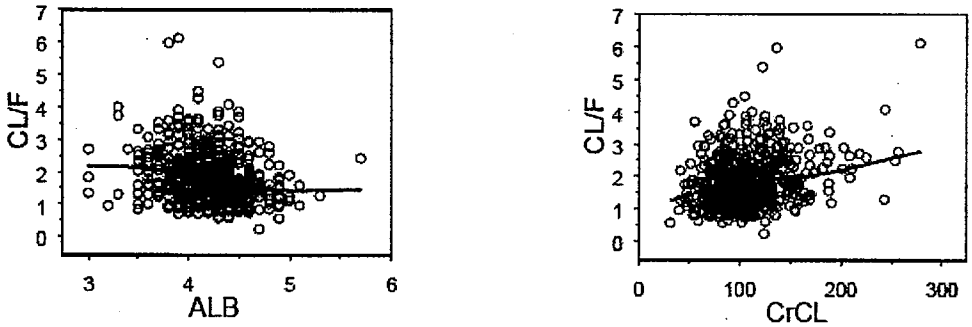


Figure 10. Empirical Bayesian Estimates of CL/F Versus ALB, ALT, AST or CrCL: Final Model (RA).

Concomitant Medications:
Disease modifying antirheumatic drugs (DMARDs), NSAIDs, and oral corticosteroids are commonly used medications for the treatment of RA. Thus, the effects of these selected concomitant medications on golimumab PK were evaluated during the covariate analysis.

In all, 392 (65.9%) subjects in the RA population PK data set received concomitant MTX, 500 (84.1%) received concomitant NSAIDs, and 332 (55.8%) received oral corticosteroids (CSTD).

Concomitant use of MTX reduced golimumab CL/F by 17.1% in the RA population PK analysis. This finding is in agreement with the observation that golimumab in combination with MTX resulted in higher steady-state trough golimumab concentrations in both C0524T05 and C0524T06, when compared to treatment with golimumab alone.

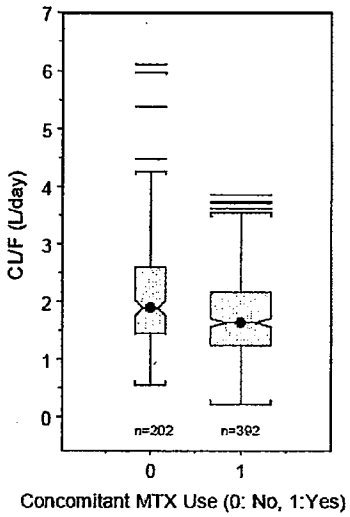
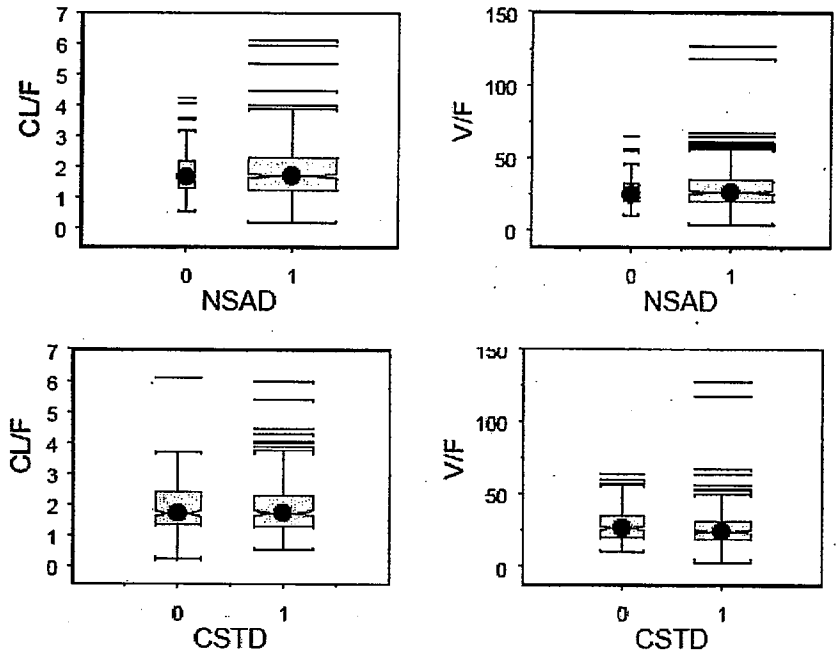


Figure 11. Empirical Bayesian Estimates of CL/F by Methotrexate Group: Final Model (RA).

Use of other concomitant medications (ie, NSAIDs or oral corticosteroids) did not significantly influence golimumab CL/F or V/F in this RA population (Figure 12).



0=no concomitant medication, 1=yes concomitant medication

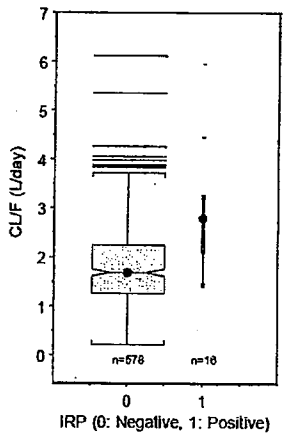
Figure 12. Empirical Bayesian Estimates of CL/F and V/F Versus NSAID (NSAD) or corticorsteroid (CSTD): Final Model (RA).

Anti-Golimumab Antibody Response:

A total of 25 subjects in Studies C0524T05 and C0524T06 tested positive for antibodies to golimumab. Of these 25 subjects, 16 had measurable serum golimumab concentrations through Week 24 and were thus included in the population PK analysis. In contrast, the remaining 9 subjects who also tested positive did not have any measurable golimumab concentrations through Week 24 and the PK of golimumab in these 9 subjects could not be characterized. As such, these 9 subjects were not included in the population PK data set.

Figure 13 shows the EBE of CL/F in subjects with RA according to antibody-to-golimumab status (i.e., positive versus negative).

Results of this analysis showed that subjects who tested positive and with measurable golimumab levels had a 29% higher CL/F than subjects who did not. Considering there were 9 subjects who did not have measurable golimumab levels, the difference between antibody negative and positive subjects may be even bigger.



(Figure Note: IRP = immune response positive)

Figure 13. Empirical Bayesian Estimates of CL/F by Antibody-to-Golimumab Status: Final Model (RA).

Other Concurrent Conditions:
The effects of several concurrent conditions (ie, hyperlipidemia, diabetes mellitus, and hypertension) as well as cigarette smoking status and use of alcohol were also assessed during the covariate analysis. In all, none of these baseline concurrent conditions had any significant effects on golimumab CL/F or V/F.

PsA:
PsA Study Description:
Study C0524T08: A multi-center, randomized, double-blind, placebo-controlled, parallel study of SC golimumab in subjects with active PsA. Eligible subjects were randomly assigned to 1 of 3 treatment groups in the placebo-controlled portion of the study (ie, Weeks 0 to 24) with a possible early-escape regimen change at Week 16:

- Group I (n =113): Placebo SC injections at Weeks 0, 4, 8, 12, 16, and 20
- Group II (n = 146): Golimumab 50 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20
- Group III (n =146): Golimumab 100 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20

At Week 16, subjects who had < 10% improvement from baseline in both swollen (SJC) and tender (TJC) joint counts entered a double-blind early escape regimen:

- Group I: switched to active treatment with golimumab 50 mg at Weeks 16 and 20
- Group II: dose increased to golimumab 100 mg at Weeks 16 and 20
- Group III: continued treatment with golimumab 100 mg at Weeks 16 and 20.

Beginning at Week 24, all subjects in Group I received golimumab 50 mg every 4 weeks while subjects in Groups II and III continued their respective golimumab dosing regimens (ie, either 50 mg or 100 mg every 4 weeks).

PK sampling scheme:

Study No.	Indication	Visit	W0	W4	W8	W12	W14	W16	W20	W24	W28
C0524T08	PsA	PK scheme	X	X	X	X	X	X	X	X	
									X		

Data

A total of 2,029 measurable serum concentrations from 337 subjects with PsA who received subcutaneous (SC) golimumab at 50 mg or 100 mg every 4 weeks in study C0524T08 were used to develop a population PK model with a nonlinear mixed-effects analysis approach. Most (60%) of the subjects in the study were male, the majority (97%) were Caucasian, the mean age was 46.8 years, and the overall duration of PsA disease was approximately 7.4 years. Most (74.4%) subjects were receiving concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and 48.9% were receiving concomitant methotrexate (MTX).

Model

A one-compartment PK model with first-order absorption and elimination was used to fit the observed PK concentration-versus-time data in study C0524T08. The model had a between subject variability (BSV) on CL/F and V/F as well as a correlation between BSV on CL/F and BSV on V/F. Residual variability was described by a proportional model.

Covariates

The effects of potential covariates on the PK parameters of golimumab were evaluated. The covariates examined included demographic characteristics, baseline hepatic and renal functions, baseline disease activity, selected concomitant medications, selected comorbidities, and antibody-to-golimumab status, etc. The final population PK data set had more covariates than NONMEM could conveniently handle one time, so GAM analysis was not used; and graphical explorations (ie, *post hoc* ETAs vs. covariates), followed by formal NONMEM estimation, were used for covariate search.

Results:

Base Model for PsA:

Table 3. Summary of Golimumab Population PK Parameter Estimates of the Base Model.

Parameters	Population estimate	95% CI[a] of population estimate	BSV[b] (CV%)[c]	95% CI[a] of BSV (CV%)[c]
CL/F (L/day)	1.65	1.55-1.75	42.2	32.1 - 52.3
V/F (L)	28.8	26.3-31.3	41.7	21.9 - 61.5
Ka (day^{-1})	0.894	0.652-1.136	NE	NE
Correlation for BSV between CL/F and V/F	0.886	-	-	-
Proportional residual variability (CV%)	29.3	27.7-30.9	12.6	0[d] - 28.1

NE (Not Estimated)
[a] 95% CI: 95% confidence interval. The lower and upper limits for 95% CI were calculated asymptotically using the standard errors estimated by the covariance step in NONMEM.
[b] BSV: Between subject variability, calculated as $(\text{variance})^{1/2}*100\%$.
[c] CV%: Coefficient of variation expressed as percent.
[d] Truncated at 0.

Final Model for PsA:

Using the Empirical Bayesian Estimate (EBE) of the ETAs in the base model, plots were generated to screen for potential covariate relationships. Of all the covariates, history of diabetes mellitus, history of hypertension, current smoking status, antibody-to-golimumab status, body weight, BSA, CRP, and CRCL appeared to have some relationship with EBE ETA for CL/F. In addition, antibody-to-golimumab status, body weight, BSA, and CRCL appeared to be correlated with EBE ETA for V/F. No covariates affected the EBE ETA for residual variability

These covariates were further evaluated using step-wise forward and backward selection method using NONMEM.

As a result, standardized body weight (ie, body weight/70 kg), standardized baseline CRP (ie, CRP/0.6 mg/dL), antibody-to-golimumab status, and current smoking status were identified as significant covariates on CL/F. Additionally, standardized body weight was a significant covariate on V/F. No covariate was significant for Ka or residual variability.

The final covariate model for CL/F can be given by the following equation:

$$CL/F(L/day)=1.38\times\left(\frac{Body\ Weight}{70}\right)^{0.778}\times\left(\frac{CRP}{0.6}\right)^{0.0575}\times 1.1^{IRP}\times 1.13^{SMOK}$$

where IRP is 1 if antibodies to golimumab were present and 0 otherwise, SMOK is 1 for current smokers and 0 otherwise.

Likewise, the final covariate model for V/F is given by the following equation:

$$V/F(L)=24.9\times\left(\frac{Body\ Weight}{70}\right)^{0.805}$$

As summarized in Table 4, the typical population value for CL/F was 1.38 L/day (95% CI: 1.30 to 1.47 L/day) and V/F was 24.9 L (95% CI: 22.7 to 26.9 L) in a typical subject with PsA weighing 70 kg. Ka was estimated to be 0.908 (day^{-1}). BSV (CV%) on CL/F and V/F was 37.6% and 37.9%, respectively. Proportional error was 29.2% (CV%) with a BSV of 13.3%. Using the typical population values of CL/F and V/F, the t1/2 of golimumab was calculated as 12.5 days.

Table 4. Summary of population pharmacokinetic parameters of golimumab and the significant covariates to golimumab PK in subjects with PsA.

Parameters	Population estimate [b]	Median [95% CI][c] of population estimate	BSV[d] (CV%)[f]	Median [95% CI][c] of BSV (CV%)
CL/F (L/day)	1.38	1.38 (1.30-1.47)	37.6	37.1 (32.9-41.2)
WGT on CL/F [f]	0.778	0.774 (0.538-1.030)	-	-
CRP on CL/F [f]	0.0575	0.0577 (0.0300-0.0859)	-	-
IRP on CL/F [f]	1.10	1.10 (0.91-1.37)	-	-
SMOK on CL/F [f]	1.13	1.13 (1.06-1.20)	-	-
V/F (L)	24.9	24.7 (22.7-26.9)	37.9	37.4 (27.2-45.4)
WGT on V/F [g]	0.805	0.796 (0.451-1.160)	-	-
Ka (day^{-1})	0.908	0.917 (0.701-1.170)	NE	-
Correlation for BSV between CL/F and V/F	0.877	0.878 (0.809-0.948)	-	-
Proportional residual variability (CV%)	29.2	29.2 (27.7-30.6)	13.3	13.3 (5.4-21.4)

NE (Note Estimated).

[a] Final population PK model in subjects with PsA was developed using data from C0524T08.

[b] Population estimates by NONMEM with the original final Phase 3 population PK dataset for the PsA population.

[c] Median [95% CI]: median value and 95% confidence interval calculated using 1,000 re-sampled and successfully converged bootstrapping runs. The lower and upper limits for 90% CI were calculated as 2.5th and 97.5th percentiles, respectively, using 1,000 re-sampled and successfully converged bootstrapping runs.

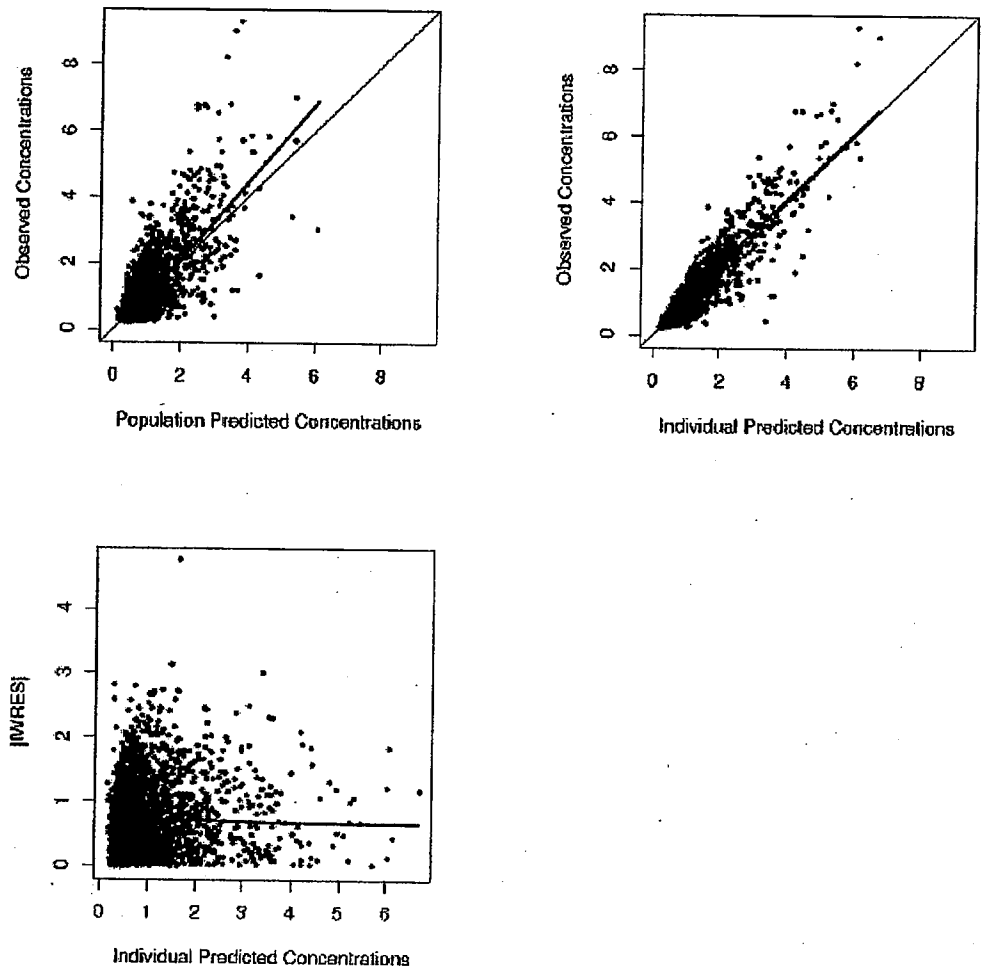
[d] BSV: Between subject variability, calculated as (variance)1/2*100%.

[e] CV%: Coefficient of variation expressed as percent.

[f] $$CL/F = 1.38 \times \left(\frac{WGT}{70}\right)^{0.778} \times \left(\frac{CRP}{0.6}\right)^{0.0575} \times 1.1^{IRP} \times 1.13^{SMOK}$$

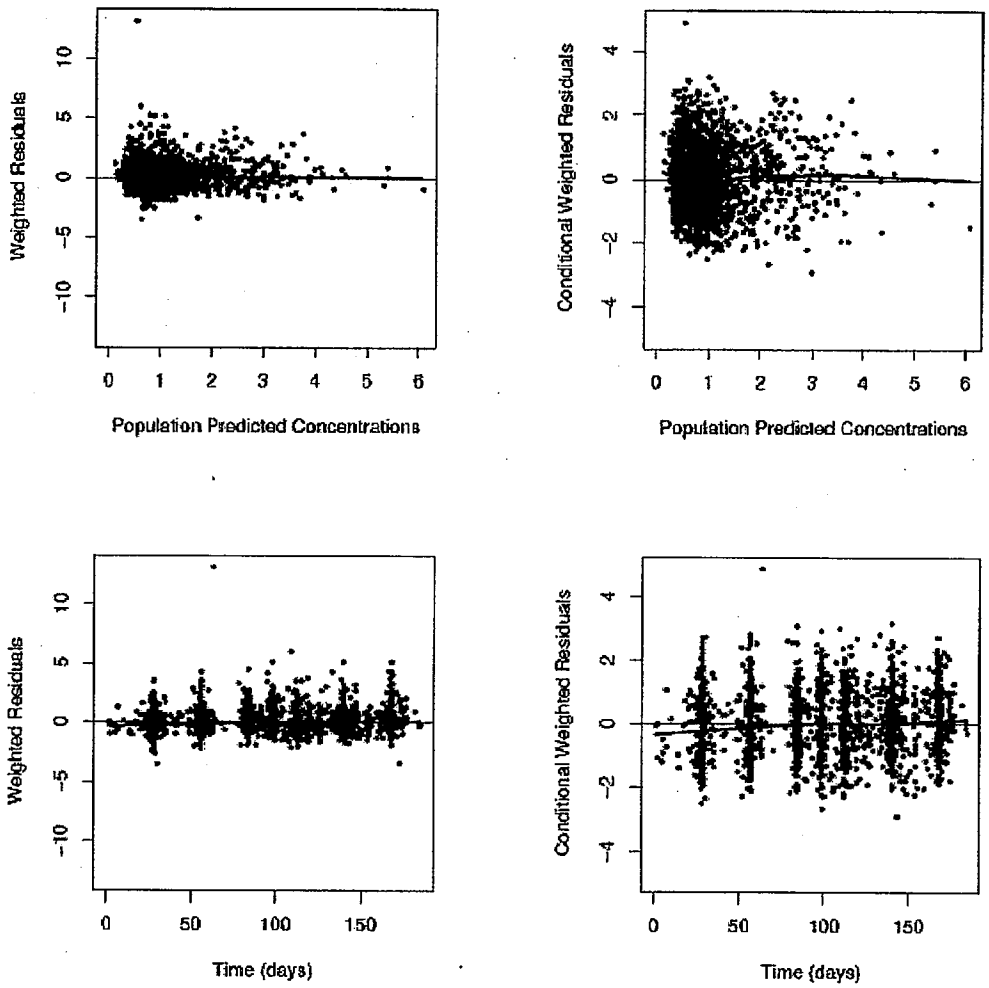
[g] $$V/F = 24.9 \times \left(\frac{WGT}{70}\right)^{0.805}$$

Figure 14 and Figure 15 show goodness of fit (GOF) plots for the final PK model. Lines of identity, zero lines, and trend lines are also overlaid as appropriate. In addition, from these GOF plots, some concentrations ≥ 6 μg/mL were underpredicted by the model. However, no serious systematic deviation was identified in the residual plots.



(Figure Notes: |IWRES| is absolute individual weighted residuals. Concentrations are in μg/mL.)

Figure 14. General Goodness of Fit for the Final Model (PsA).



(Figure Notes: Left and right panels are weighted residuals and conditional weighted residuals, respectively. Concentrations are in μg/mL.)

Figure 15. Residual Goodness of Fit for the Final Model (PsA).

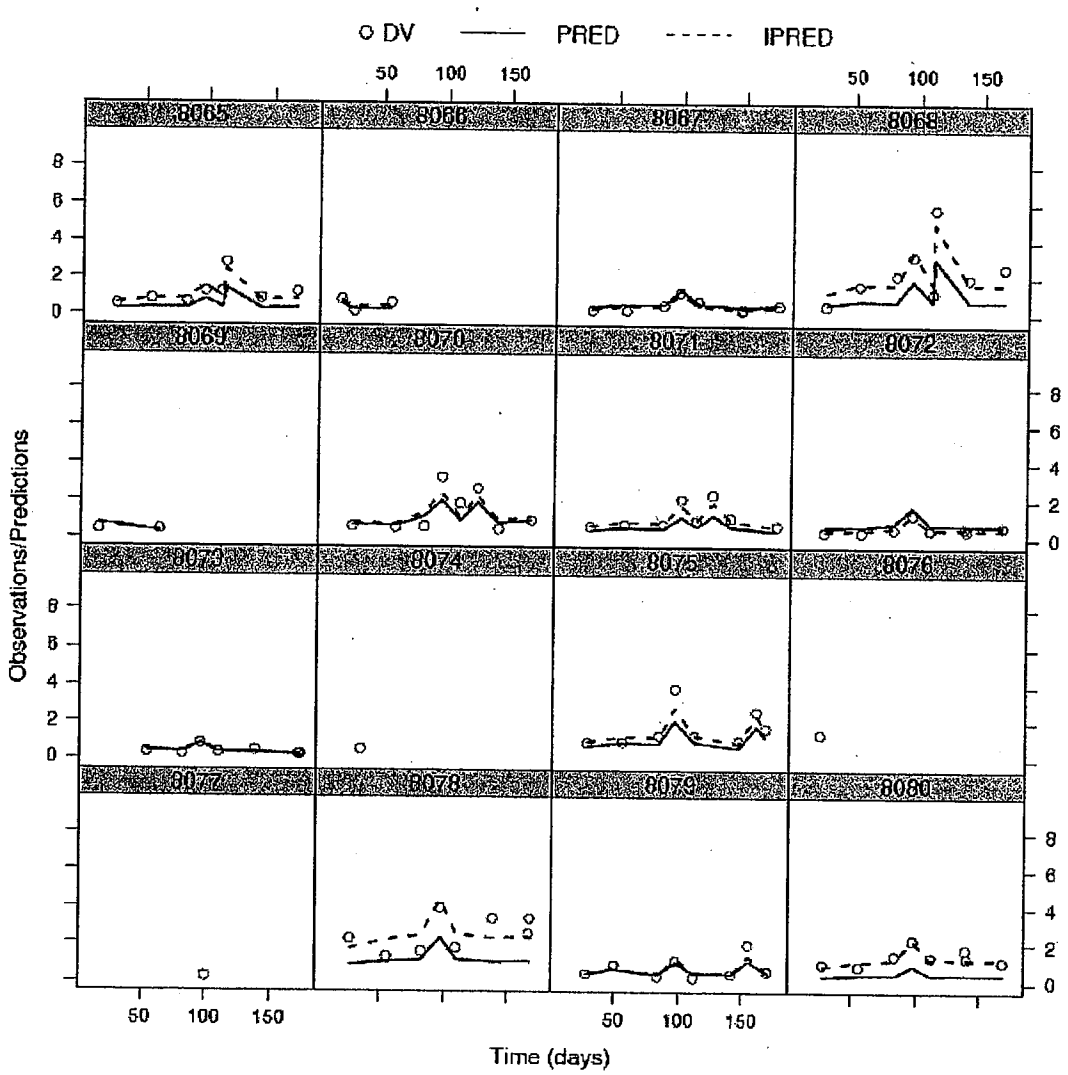


Figure 16. Selected Individual Observed (DV), Model Predicted (PRED), and Individual Predicted (IPRED) Concentration-Time Plots for Subjects in the Population PK Data Set: Final Model (PsA). Concentrations are in µg/mL.

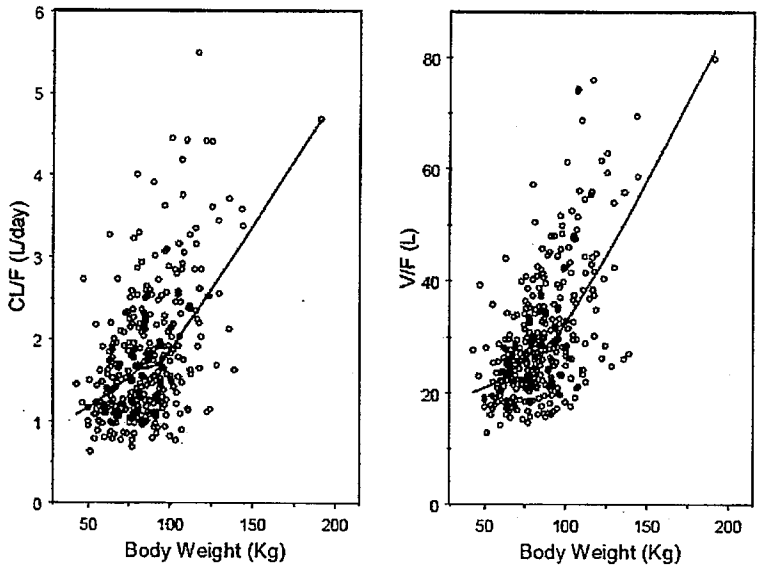
Effect of Covariates on Golimumab PK Parameters:

Demographics:

Several demographic characteristics were evaluated as potential covariates including body weight, age, sex, and race. Of these, body weight was the most significant covariate identified for both CL/F and V/F of golimumab. For the 337 subjects with PsA in this population PK, the mean

body weight was 85.4 kg (range: 43.0 to 191 kg). Both CL/F and V/F increased with body weight (Figure 17).

a. Body Weight:



(Figure Note: LOESS trend lines are overlaid in the plots.)

Figure 17. Empirical Bayesian Estimates of CL/F and V/F Versus Body Weight: Final Model (PsA).

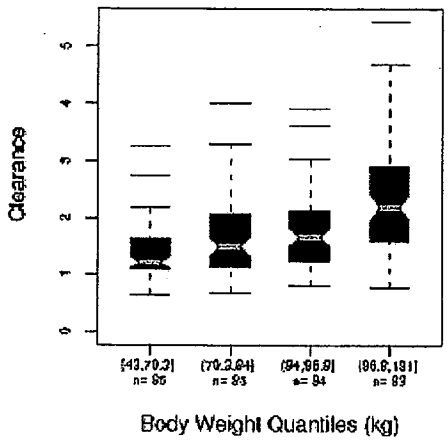


Figure 18. Empirical Bayesian Estimates of CL/F by Body Weight Quartiles: Final Model (PsA)

These Monte Carlo simulations showed that, following SC administration of golimumab 50 mg every 4 weeks, median steady-state trough serum golimumab concentration for subjects > 100 kg was 26.5% lower than that for subjects ≤ 100 kg (ie, 0.36 μg/mL vs 0.49 μg/mL, respectively).

b. Age

The effect of age on CL/F and V/F was evaluated in the covariate analysis. For the 337 subjects in the PsA data set, the mean age was 47 years (range: 20 to 78 years). Of these 337 subjects, 16 (4.7%) were more than 65 years of age. Results of covariate analysis showed that age did not influence either of these 2 PK parameters.

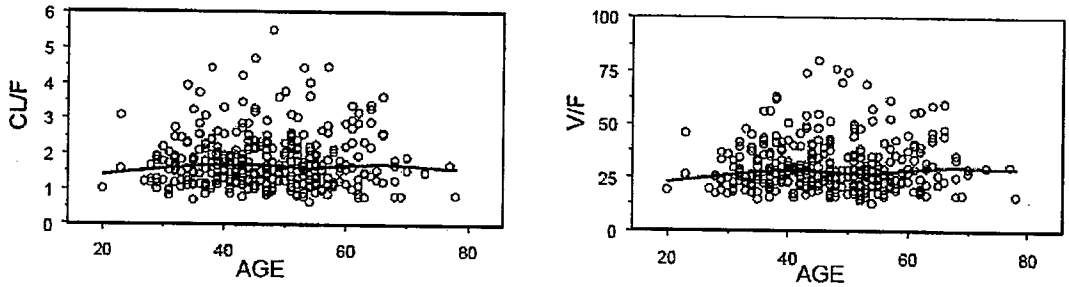
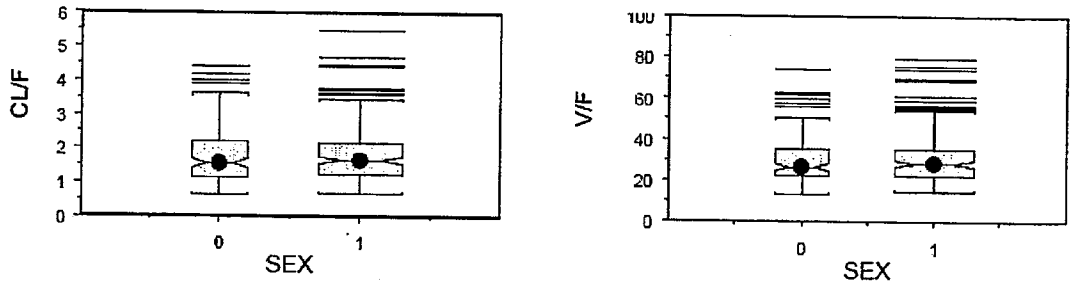


Figure 19. Empirical Bayesian Estimates of CL/F and V/F Versus Age: Final Model (PsA).

c. Gender

Sex was evaluated as a potential covariate in this population PK analysis. Of the 337 subjects in the PsA data set, 202 (59.9%) were male. Results of the covariate analysis showed that, after body weight adjustment, sex did not significantly influence CL/F or V/F.



SEX (0=female, 1=male)

Figure 20. Empirical Bayesian Estimates of CL/F and V/F Versus Age: Final Model (PsA).

d. Race

Race was evaluated as a potential covariate on CL/F and V/F. However, of the 337 subjects in this PsA data set, 326 (96.7%) were Caucasian. Thus, in this population, the effect of race on golimumab PK could not be assessed.

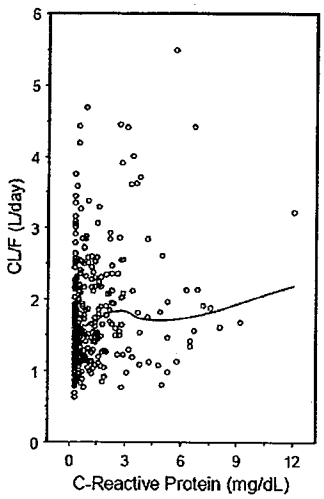
Baseline disease activities:

Several baseline disease characteristics were assessed as potentially important covariates for

golimumab PK. For this PsA population analysis, baseline DAS28C, SJC, TJC, CRP, and PASI score were each evaluated for potential effects on CL/F and V/F. Of these baseline measures, CRP was identified as a significant covariate for golimumab CL/F.

For the 337 subjects with PsA in this analysis, the median baseline CRP was 0.6 mg/dL with an interquartile range of 0.4 to 2.5 mg/dL. As indicated by the small value (ie, 0.0575) for the exponent of CRP on CL/F in the final covariate model for CL/F, however, CRP level only had a weak correlation with the EBE of CL/F. Therefore, baseline CRP levels would not provide significant predictability for CL/F and the impact of baseline CRP on steady-state golimumab exposure would not be clinically important.

Figure 21 shows a scatter plot of the EBE of CL/F versus CRP in subjects with PsA.



(Figure Note: LOESS trend line is overlaid in the plot.)

Figure 21. Empirical Bayesian Estimates of CL/F Versus C-Reactive Protein: Final Model (PsA)

Hepatic or Renal Functions:
For this population PK analysis, baseline ALT, AST, and serum ALB were used as indicators of hepatic function and baseline CRCL was used as an indicator of renal function. The potential effects of each of these baseline covariates on golimumab PK were systematically evaluated.

The majority of subjects had normal hepatic function (ie, overall baseline values of ALT, AST, and ALB were generally within normal ranges). For example, the mean ± SD for ALT, AST, and ALB were 25.9 ± 14.3 U/L, 22.3 ± 8.1 U/L, and 4.3 ± 0.3 g/dL, respectively. Likewise the majority of subjects had normal renal function. That is, the estimated mean baseline CRCL was 122.2 mL/min (range: 50.6 to 258.8 mL/min) for the 337 subjects in the PsA data set.

In all, the covariate analysis indicated that baseline ALT, AST, ALB, and CRCL had no significant effects on either CL/F or V/F of golimumab.

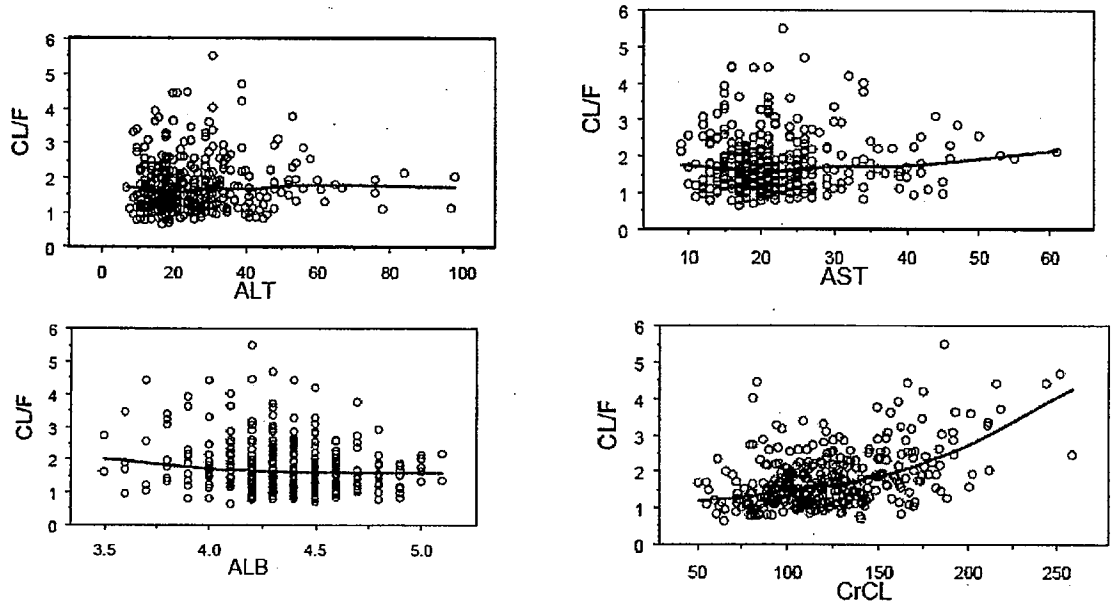
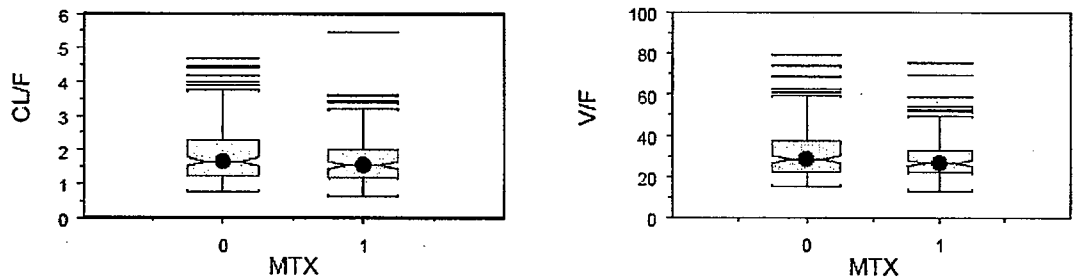
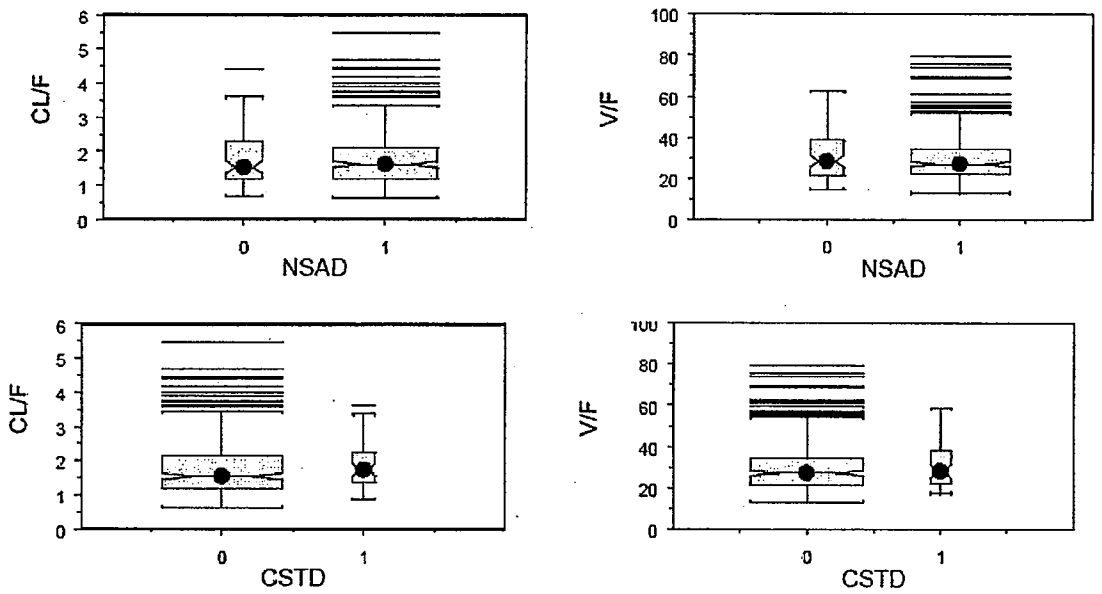


Figure 22. Empirical Bayesian Estimates of CL/F Versus ALB, ALT, AST or CrCL: Final Model (PsA).

Concomitant Medications:
Disease modifying antirheumatic drugs (DMARDs), NSAIDS, and oral corticosteroids are commonly used medications for the treatment of PsA. Thus, the effects of these selected concomitant medications on golimumab PK were evaluated in the covariate analysis.

A total of 165 (48.9%) subjects in the PsA population PK data set received concomitant MTX; 251 (74.4%) received concomitant NSAIDs, and 53 (15.7%) received oral corticosteroids. Overall, the results of the population PK analysis showed that the concomitant use of MTX, NSAIDs, or oral corticosteroids did not significantly influence golimumab CL/F.





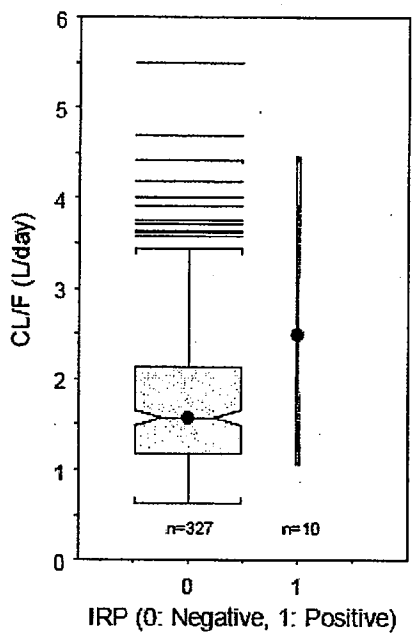
0=no concomitant medication, 1=yes concomitant medication

Figure 23. Empirical Bayesian Estimates of CL/F and V/F Versus Methotrexate (MTX), NSAID (NSAD) or cotrocorseroid (CSTD): Final Model (PsA).

Anti-Golimumab Antibody Response:

A total of 13 subjects in study C0524T08 tested positive for antibodies to golimumab. Ten of these 13 subjects had measurable serum golimumab concentrations through Week 24 and were thus included in the population PK data set. In contrast, the remaining 3 subjects who also tested positive did not have any measurable golimumab concentrations through Week 24 and the PK of golimumab in these 3 subjects could not be characterized. As such, these 3 subjects were not included in the population PK data set.

Figure 24 shows the EBE of CL/F in subjects with PsA according to antibody-to-golimumab status (i.e., positive versus negative). Results of this analysis showed that subjects who tested positive with measurable golimumab levels had a 10% higher CL/F than subjects who did not. However, since relatively few (n = 10) subjects in this PK analysis population tested positive, the impact of antibody status may not be accurately quantified. Considering there were 3 subjects who did not have measurable golimumab levels, the difference between antibody negative and positive subjects may be even bigger.



(Figure Note: IRP = antibody-to-golimumab status [ie, immune response positive].)

Figure 24. Empirical Bayesian Estimates of CL/F by Antibody-to-Golimumab Status: Final Model (PsA).

Other Concurrent Conditions:
The effects of several concurrent conditions (ie, hyperlipidemia, diabetes mellitus, and hypertension) as well as cigarette smoking status and use of alcohol were also assessed during the covariate analysis. Except for smoking status, none of these other baseline concurrent conditions had any significant effects on golimumab CL/F or V/F.

A total of 61 (18.1%) of subjects in the PsA data set were current smokers. Compared to nonsmokers, subjects with PsA who were smokers had an estimated 13% higher CL/F of golimumab. To date, it has not been reported whether cigarette smoking can influence the disposition of monoclonal antibodies, although smoking is known to induce CYP1A2-mediated drug metabolism for small molecular drugs.

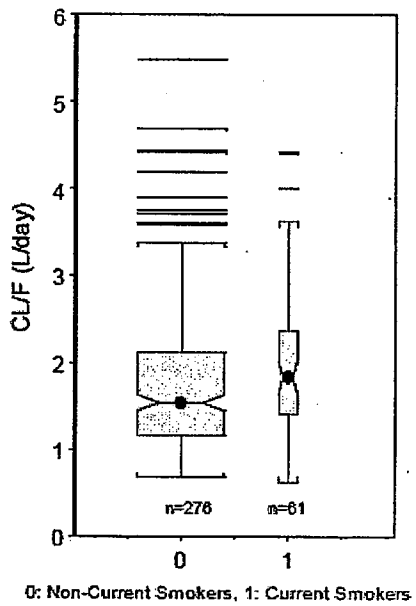


Figure 25. Empirical Bayesian Estimates of CL/F by Smoking Status: Final Model (PsA).

AS:

AS Study Description:

Study C0524T09: A multicenter, randomized, double-blind, placebo-controlled, parallel study of golimumab SC injections in subjects with active AS. Eligible subjects were randomly assigned to 1 of the following 3 treatment groups in the placebocontrolled portion of the study (ie, Weeks 0 to 24) with a possible early-escape regimen change at Week 16:

- Group I (n = 78): Placebo SC injections at Weeks 0, 4, 8, 12, 16, and 20
- Group II (n = 138): Golimumab 50 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20
- Group III (n = 140): Golimumab 100 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20

At Week 16, subjects with < 20% improvement from baseline in both total back pain and morning stiffness measures entered a double-blind early escape regimen:

- Group I: switched to active treatment with golimumab 50 mg at Weeks 16 and 20
- Group II: dose increased to golimumab 100 mg at Weeks 16 and 20
- Group III: continued treatment with golimumab 100 mg at Weeks 16 and 20.

Beginning at Week 24, all subjects in Group I received golimumab 50 mg every 4 weeks while subjects in Groups II and III continued their respective golimumab dosing regimens (ie, either 50 mg or 100 mg every 4 weeks).

PK sampling scheme:

Study No.	Indication	Visit	W0	W4	W8	W12	W14	W16	W20	W24	W28
C0524T09	AS	PK scheme	X	X	X	X	X	X	X	X	
									X		

Data

A total of 1,983 measurable serum concentrations from 312 subjects with AS who received subcutaneous (SC) golimumab at 50 mg or 100 mg every 4 weeks in study C0524T09 were used to develop a population PK model with a nonlinear mixed-effects analysis approach. Most (72.1%) of the subjects in the study were male, the majority (73.3%) were Caucasian, the mean age was 39.2 years, and the overall duration of AS disease was approximately 8.5 years. Most (88.7%) subjects were receiving concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) while 26.6% were receiving concomitant sulfasalazine (SSZ), and 20.5% were using methotrexate (MTX).

Model

A one-compartment PK model with first-order absorption and elimination was used to fit the observed PK concentration-versus-time data in study C0524T09. The model had a between subject variability (BSV) on CL/F, V/F, and first-order absorption rate constant (Ka) as well as a correlation between BSV on CL/F and BSV on V/F. Residual variability was described by a combined additive and proportional model with a BSV term.

Covariates

The effects of potential covariates on the PK parameters of golimumab were evaluated. The covariates examined included demographic characteristics, baseline hepatic and renal functions, baseline disease activity, selected concomitant medications, selected comorbidities, and antibody-to-golimumab status, etc. The final population PK data set had more covariates than NONMEM could conveniently handle one time, so GAM analysis was not used; and graphical explorations (ie, post hoc ETAs vs. covariates), followed by formal NONMEM estimation, were used for covariate search.

Results:

Base Model for AS:

Table 5. Summary of Golimumab Population PK Parameter Estimates of the Base Model for AS.

Parameters	Population estimate	95% CI[a] of population estimate	BSV[b] (CV%)[c]	95% CI[a] of BSV (CV%)[c]
CL/F (L/day)	1.38	1.30-1.46	42.1	32.1-52.0
V/F (L)	24.1	22.2-26.0	43.2	26.3-60.2
Ka (day^{-1})	1.000	0.686-1.314	75.4	9.3-141.4
Correlation for BSV between CL/F and V/F	0.846	-	-	-
Additive residual variability (SD, μg/mL)	0.059	0.0251-0.0867	15.8	0.1-31.6
Proportional residual variability (CV%)	24.0	21.8-26.2		

[a] 95% CI: 95% confidence interval. The lower and upper limits for 95% CI were calculated asymptotically using the standard errors estimated by the covariance step in NONMEM.
[b] BSV: Between subject variability, calculated as $(\text{variance})^{1/2}*100\%$.
[c] CV%: Coefficient of variation expressed as percent.

Final Model for AS:

Using the Empirical Bayesian Estimate (EBE) of the ETAs in the base model, plots were generated to screen for potential covariate relationships. Of all the covariates, sex, history of diabetes mellitus, concomitant medications (ie, SSZ, HCQ or oral corticosteroids), antibody-to-golimumab status, body weight, BSA, CRP, ALB, and CRCL appeared to have some relationship with EBE of ETA for CL/F. In addition, antibody-to-golimumab status, concomitant medications (ie, MTX, SSZ, HCQ, or corticosteroids), body weight, BSA, ALB, and CRCL appeared to be correlated with EBE of ETA for V/F. No covariates were correlated with EBE of ETA for residual variability.

These covariates were further evaluated using step-wise forward and backward selection method using NONMEM.

As a result, standardized body weight (ie, body weight/70 kg), standardized baseline CRP (ie, CRP/1.0 mg/dL), antibody-to-golimumab status, and sex were identified as significant covariates on CL/F. Additionally, standardized body weight was a significant covariate on V/F. No covariate was significant for Ka or residual variability.b v

The final covariate model for CL/F can be given by the following equation:

$$CL/F\,(L/day) = 1.41 \times \left(\frac{Body\ Weight}{70}\right)^{0.839} \times \left(\frac{CRP}{1.0}\right)^{0.05} \times 1.36^{IRP} \times 0.874^{SEX}$$

where IRP is 1 if antibodies to golimumab were present and 0 otherwise, SEX is 1 for male and 0 for female.

Likewise, the final covariate model for V/F is given by the following equation:

$$V/F(L)=22.6\times\left(\frac{Body\ Weight}{70}\right)^{0.801}$$

As summarized in Table 6, the typical population value for CL/F was 1.41 L/day (95% CI: 1.31 to 1.51 L/day) and V/F was 22.6 L (20.7 to 24.4 L) in a typical subject with AS weighing 70 kg. Ka was estimated to be 1.010 (day^{-1}). BSV (CV%) on CL/F, V/F, and Ka was 35.2%, 38.6%, and 78.6%, respectively. Additive residual variability was 0.0621 µg/mL (SD) and proportional residual variability was 23.7% (CV%) with a BSV of 16.0%. Using the typical population values of CL/F and V/F, the t1/2 of golimumab was calculated as 11.1 days.

Table 6. Summary of population pharmacokinetic parameters of golimumab and the significant covariates to golimumab PK in subjects with AS.

Parameters	Population estimate [b]	Median [95% CI][c] of population estimate	BSV[d] (CV%)[e]	Median [95% CI][c] of BSV (CV%)
CL/F (L/day)	1.41	1.40 (1.31-1.51)	35.2	34.9 (30.2-39.5)
WGT on CL/F[f]	0.839	0.837 (0.635-1.050)	-	-
CRP on CL/F[f]	0.0500	0.0513 (0.0209-0.0816)	-	-
IRP on CL/F[f]	1.36	1.36 (1.19-1.76)	-	-
SEX on CL/F[f]	0.874	0.874 (0.816-0.935)	-	-
V/F (L)	22.6	22.6 (20.7-24.4)	38.6	38.5 (28.2-46.9)
WGT on V/F[g]	0.801	0.803 (0.496-1.100)	-	-
Ka (day^{-1})	1.010	1.020 (0.760-1.460)	78.6	77.7 (30.5-107.7)
Correlation for BSV between CL/F and V/F	0.787	0.792 (0.680-0.861)	-	-
Additive residual variability (SD, µg/mL)	0.0621	0.0625 (0.0270-0.0897)	16.0	15.2 (5.2-23.0)
Proportional residual variability (CV%)	23.7	23.7 (21.5-25.9)		

[a] Final population PK model in subjects with AS was developed using data from C0524T09.

[b] Population estimates by NONMEM with the original final Phase 3 AS PK dataset.

[c] Median [95% CI]: median value and 95% confidence interval calculated using 1,000 re-sampled and successfully converged bootstrapping runs. The lower and upper limits for 90% CI were calculated as 2.5th and 97.5th percentiles, respectively, using 1,000 re-sampled and successfully converged bootstrapping runs.

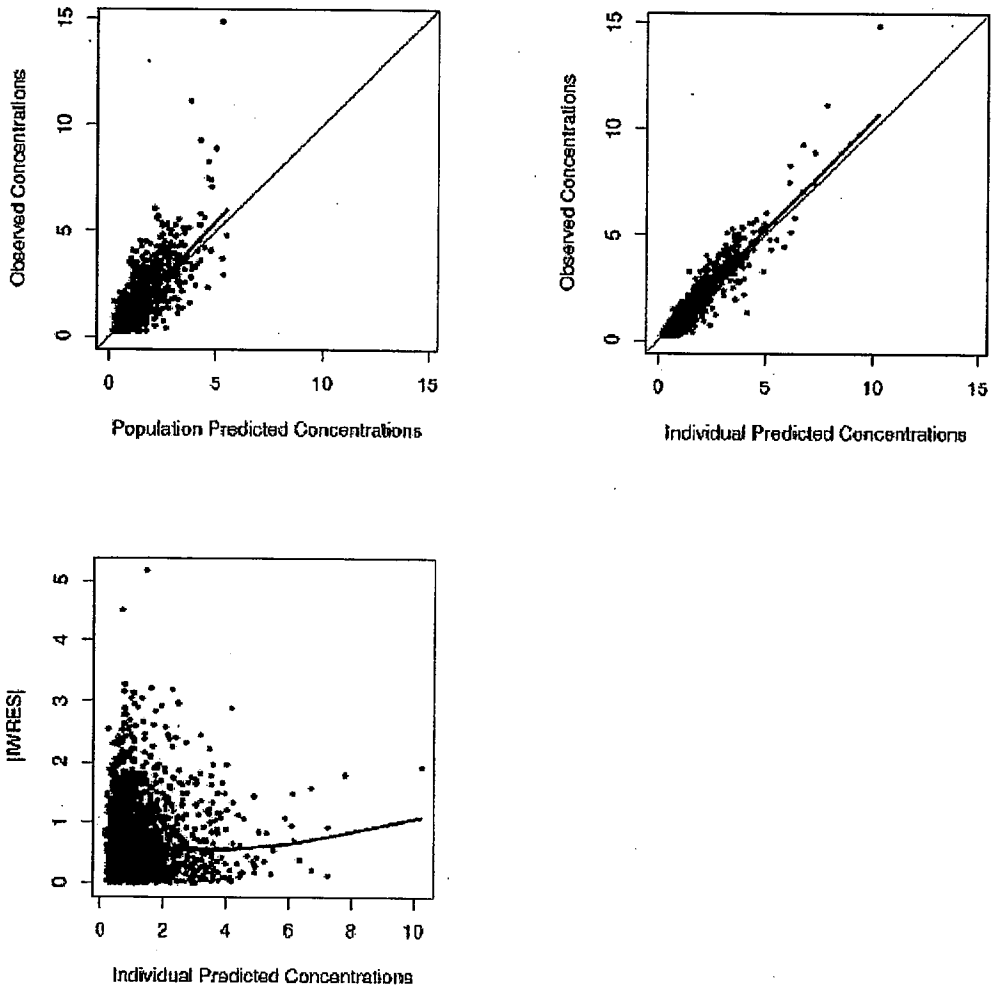
[d] BSV: Between subject variability, calculated as $(variance)^{1/2}*100\%$.

[e] CV%: Coefficient of variation expressed as percent.

[f] $CL/F=1.41\times\left(\frac{WGT}{70}\right)^{0.839}\times\left(\frac{CRP}{1.0}\right)^{0.05}\times 1.36^{IRP}\times 0.874^{SEX}$

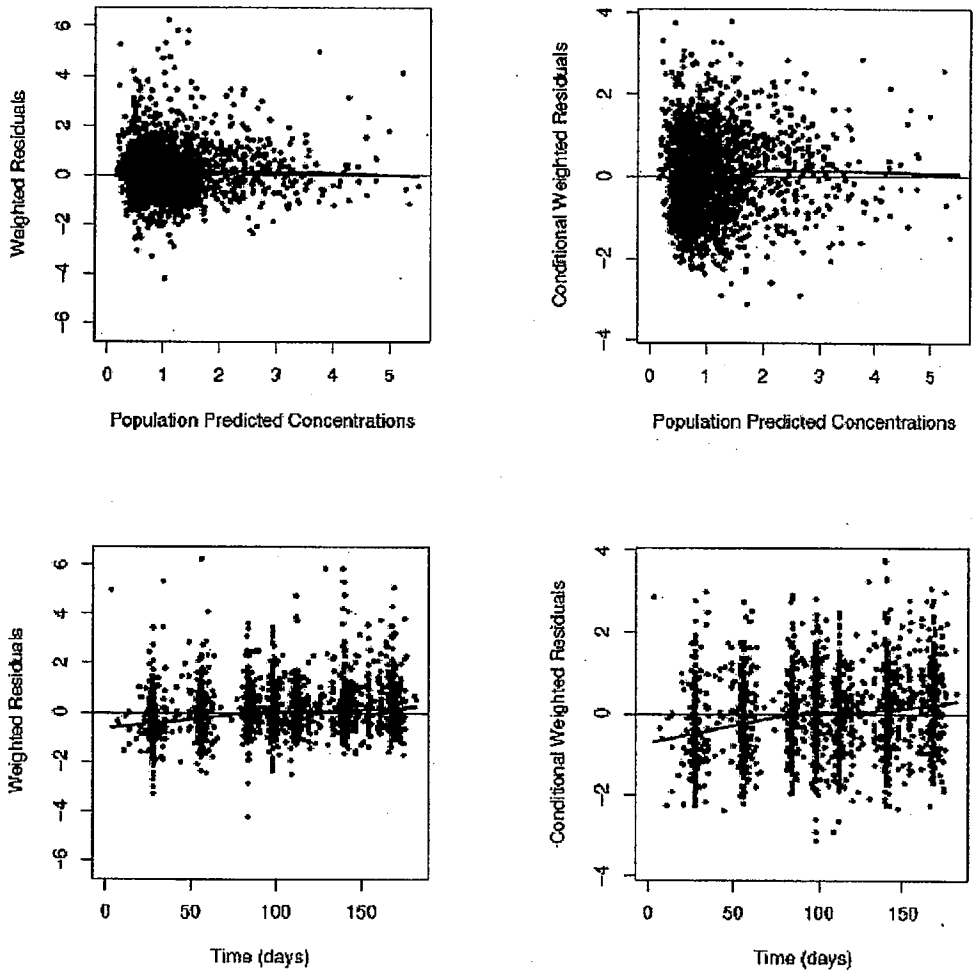
[g] $V/F=22.6\times\left(\frac{WGT}{70}\right)^{0.801}$

Figure 26 and Figure 27 show goodness of fit (GOF) plots for the final PK model. Lines of identity, zero lines, and trend lines are also overlaid as appropriate. In addition, from these GOF plots, some concentrations ≥ 8 μg/mL were underpredicted by the model. However, no serious systematic deviation was identified in the residual plots.



(Figure Notes: |IWRES| is absolute individual weighted residuals. Concentrations are in μg/mL.)

Figure 26. General Goodness of Fit for the Final Model (AS).



(Figure Notes: Left and right columns represent weighted residuals and conditional weighted residuals, respectively. Concentrations are in µg/mL.)

Figure 27. Residual Goodness of Fit for the Final Model (AS).

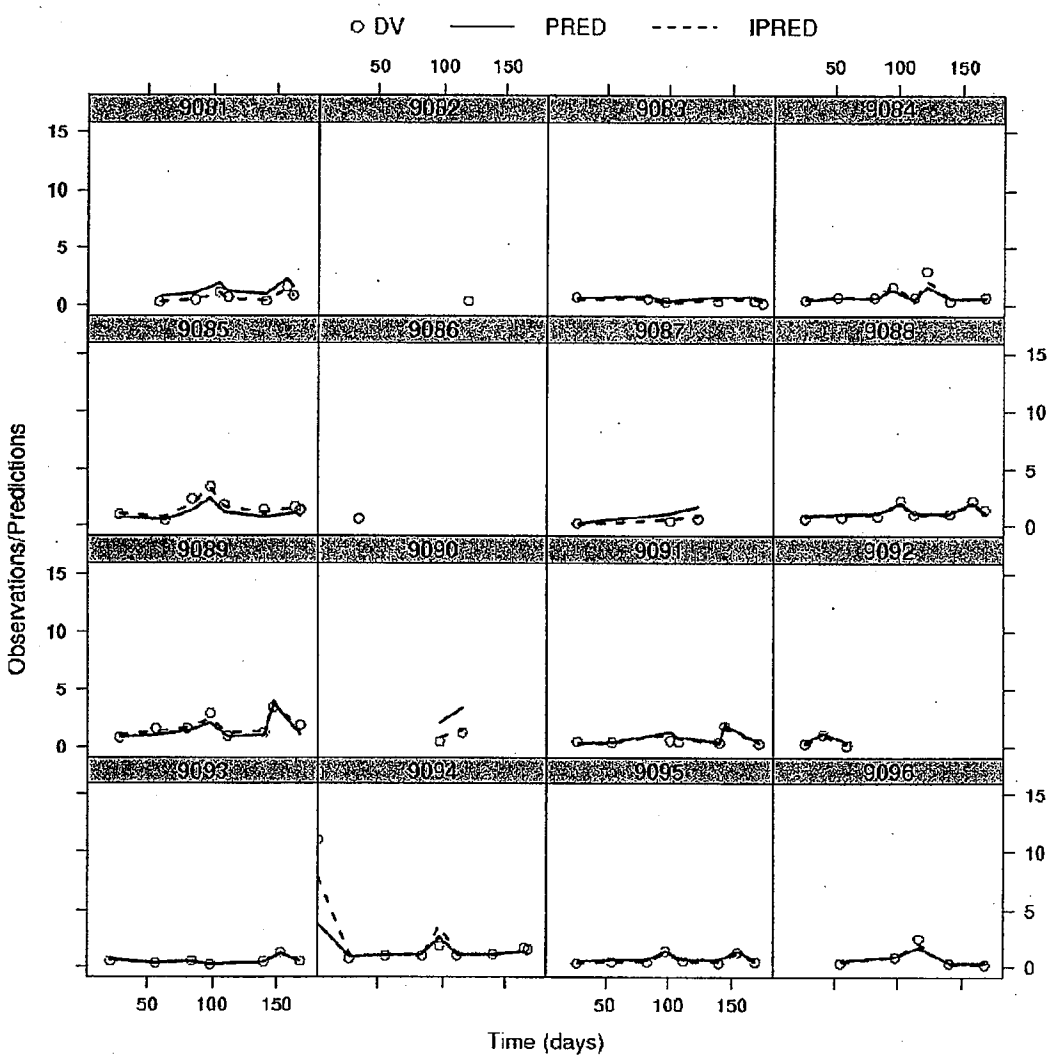


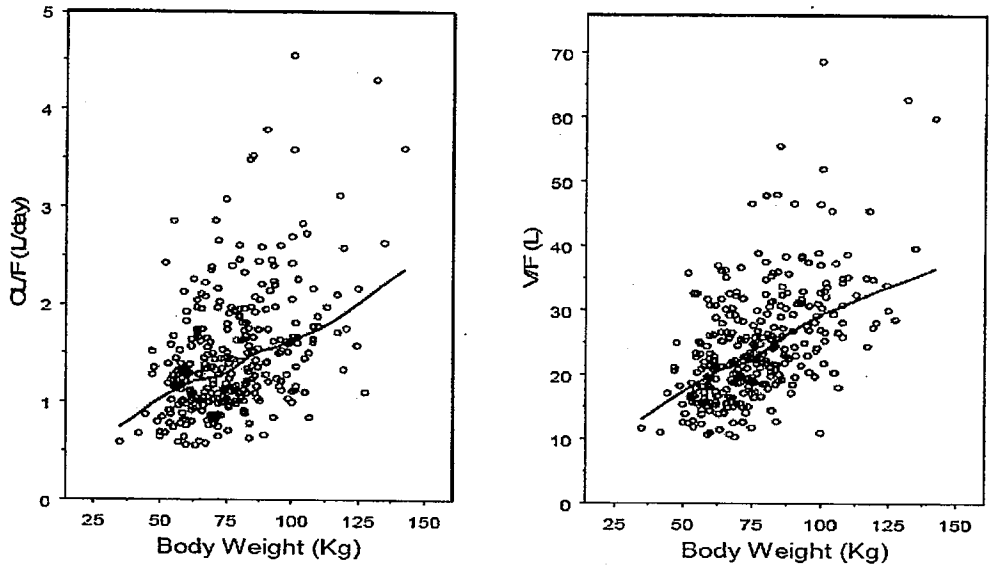
Figure 28. Selected Individual Observed (DV), Model Predicted (PRED), and Individual Predicted (IPRED) Concentration-Time Plots for Subjects in the Population PK Data Set: Final Model (AS). Concentrations are in µg/mL.

Effect of Covariates on Golimumab PK Parameters:

Demographics:

Several demographic characteristics were evaluated as potential covariates including body weight, age, sex, and race. Of these, body weight was the most significant covariate identified for both CL/F and V/F of golimumab. For the 312 subjects with AS in this population PK analysis, the mean body weight was 77.2 kg (range: 35.0 to 142.4). Both CL/F and V/F increased with body weight (Figure 29).

a. Body Weight:



(Figure Note: LOESS trend lines are overlaid in the plots.)

Figure 29. Empirical Bayesian Estimates of CL/F and V/F Versus Body Weight: Final Model (AS).

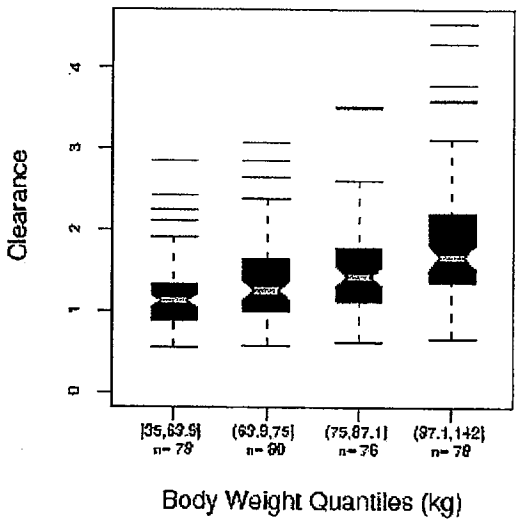


Figure 30. Empirical Bayesian Estimates of CL/F by Body Weight Quartiles: Final Model (AS).

These Monte Carlo simulations showed that, following SC administration of golimumab 50 mg every 4 weeks, median steady-state trough serum golimumab concentration for subjects weighing > 100 kg was 29.8% lower than that for subjects ≤ 100 kg (ie, 0.40 μg/mL versus 0.57 μg/mL, respectively).

b. Age

The effect of age on CL/F and V/F was evaluated in the covariate analysis. For the 312 subjects in the AS data set, the mean age was 39 years (range: 18 to 83 years). Of these 312 subjects, 7 (2.2%) were more than 65 years of age. Results of this analysis showed that age did not influence either of these 2 PK parameters.

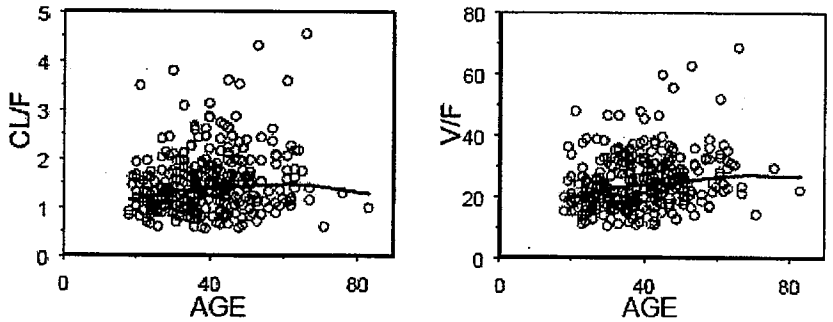
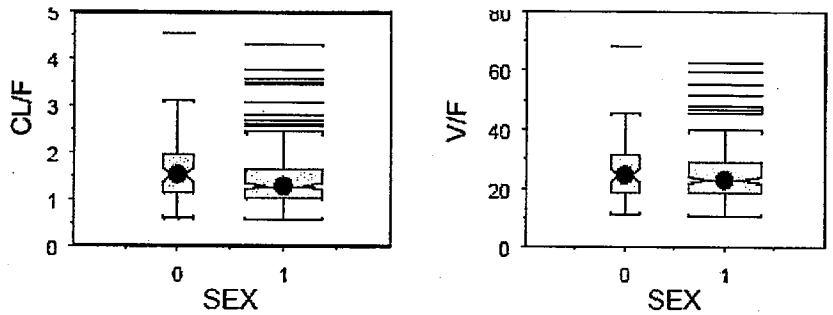


Figure 31. Empirical Bayesian Estimates of CL/F and V/F Versus Age: Final Model (AS).

c. Gender

Sex was evaluated as a potential covariate in this population PK analysis. Of the 312 subjects in this AS data set, 225 (72.1%) were male. Results of the covariate analysis showed that, after body weight adjustment, female subjects with AS had a 13% higher CL/F than male subjects with AS. In contrast, sex did not appear to affect V/F once an adjustment for body weight was made.

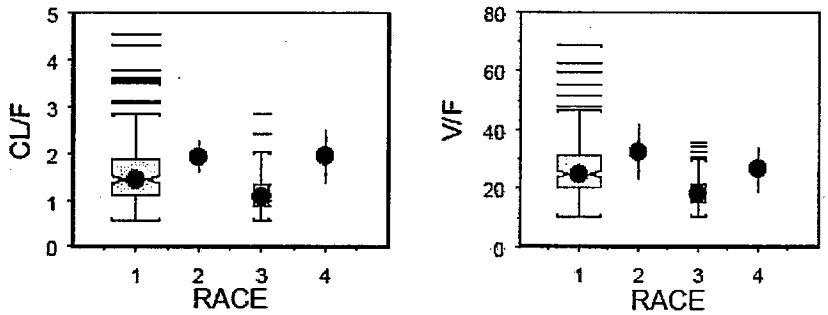


SEX (0=female, 1=male)

Figure 32. Empirical Bayesian Estimates of CL/F and V/F Versus Age: Final Model (AS).

d. Race

Race was also evaluated as a potential covariate on CL/F and V/F. Of the 312 subjects in this AS data set, 229 (73.3%) were Caucasian, 76 (24.3%) were Asian, 3 (0.9%) were Black, and 4 (1.2%) were of other races. The sample sizes for the Caucasian and Asian groups were adequate for an ethnic comparison. The results showed the golimumab PK parameters were not significantly different between these 2 groups.



RACE (1=Caucasian, 2=Black, 3=Asian, 4=Other);

Figure 33. Empirical Bayesian Estimates of CL/F and V/F Versus Race: Final Model (AS).

Baseline disease activities:

Several baseline disease characteristics were assessed as potentially important covariates for golimumab PK. For this population PK analysis in subjects with AS, baseline BASDAI score, CRP level, and disease duration (in years, from the date of initial diagnosis) were evaluated for their potential effects on golimumab CL/F and V/F. Of these 3 baseline measures, CRP was identified as a significant covariate for golimumab CL/F.

For the 312 subjects with AS in this analysis, the median baseline CRP was 1.0 mg/dL with an interquartile range of 0.4 to 2.5 mg/dL. As indicated by the small value (ie, 0.05) for the exponent of CRP on CL/F in the final covariate model for CL/F, however, CRP level only had a weak correlation with the EBE of CL/F. Therefore, baseline CRP levels would not provide significant predictability for CL/F and the impact of baseline CRP on steady-state golimumab exposure would not be clinically important.

Figure 34 shows a scatter plot of the EBE of CL/F versus CRP in subjects with AS.

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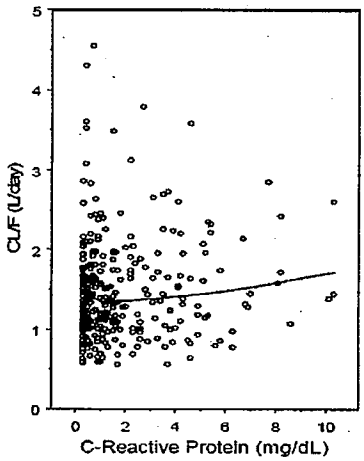


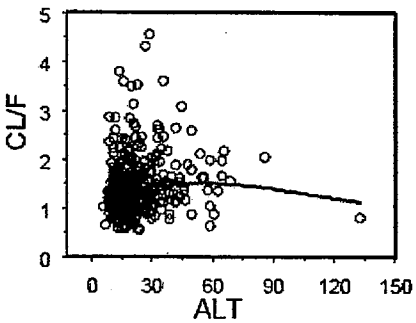
(Figure Note: LOESS trend line is overlaid in the plot.)

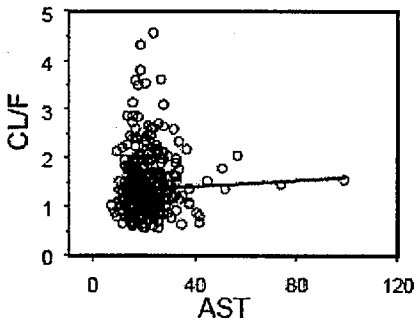
Figure 34. Empirical Bayesian Estimates of CL/F Versus C-Reactive Protein: Final Model (AS).

Hepatic or Renal Functions:
For this population PK analysis, baseline ALT, AST and serum ALB were used as indicators of hepatic function and baseline CRCL was used as an indicator of renal function. The potential effects of each of these baseline covariates on golimumab PK were systematically evaluated.

The majority of subjects had normal hepatic function (ie, overall baseline values of ALT, AST, and ALB were generally within normal ranges). For example, the mean ± SD for ALT, AST, and ALB were 23.7 ± 14.2 U/L, 22.0 ± 8.9 U/L, and 4.4 ± 0.3 g/dL, respectively. Likewise, the majority of subjects had normal renal function. That is, the estimated mean baseline CRCL was 125.2 mL/min (range: 47.6 to 215.9 mL/min) for the 312 subjects in the AS data set.

In all, the covariate analysis indicated that baseline ALT, AST, ALB, and CRCL had no significant effects on either CL/F or V/F of golimumab.





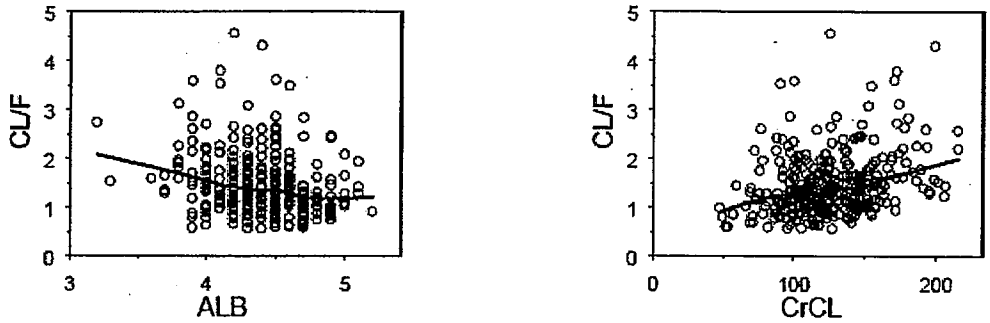


Figure 35. Empirical Bayesian Estimates of CL/F Versus ALB, ALT, AST or CrCL: Final Model (AS).

Concomitant Medications:
Disease modifying antirheumatic drugs (DMARDs), NSAIDs, and oral corticosteroids are commonly used medications for the treatment of AS. Thus, the effects of these selected concomitant medications on golimumab PK were evaluated during the covariate analysis.

A total of 64 (20.5%) subjects in the AS population PK data set received concomitant MTX, 277 (88.7%) received concomitant NSAIDs, and 50 (16.0%) received oral corticosteroids.

Overall, the results of the population PK analysis showed that concomitant use of MTX, NSAIDS, or oral corticosteroids did not significantly influence golimumab CL/F.

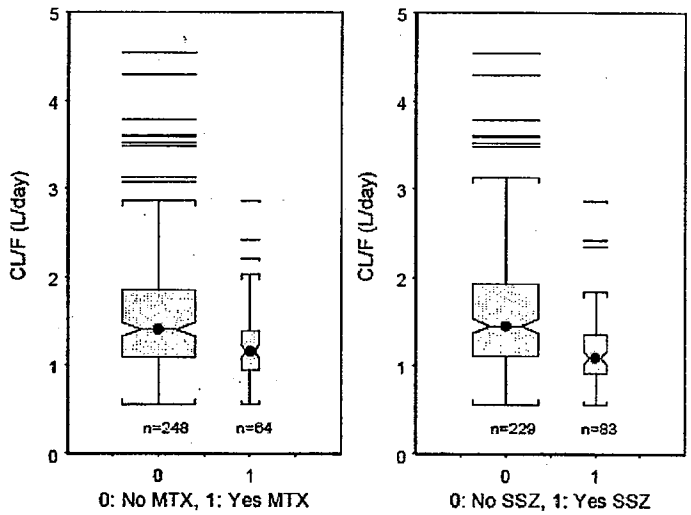
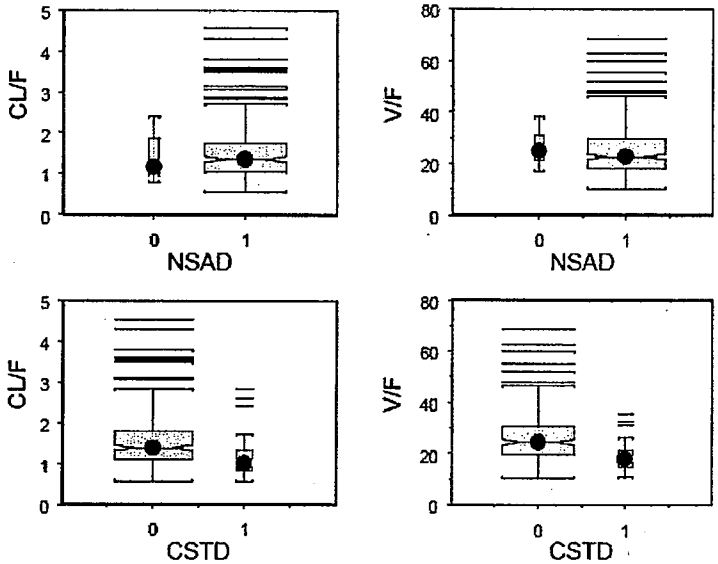


Figure 36. Empirical Bayesian Estimates of CL/F or V/F by Methotrexate (MTX) and Sulfasalazine (SSZ) Group: Final Model (AS).

Two other DMARDs, SSZ and HCQ were allowed in study C0524T09. A total of 83 (26.6%) subjects received SSZ, and 3 (0.9%) received HCQ. Results of the covariate analysis showed that

while the concomitant use of SSZ did not significantly influence CL/F in subjects with AS, the effect of HCQ on golimumab PK could not be assessed due to the limited number of subjects receiving HCQ.



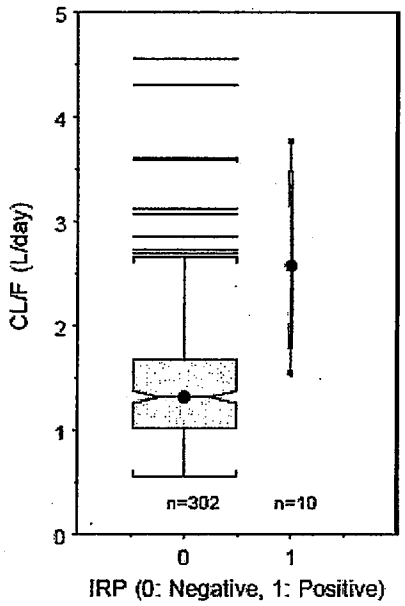
0=no concomitant medication, 1=yes concomitant medication

Figure 37. Empirical Bayesian Estimates of CL/F and V/F Versus NSAID (NSAD) or Corticorsteroid (CSTD): Final Model.

Anti-Golimumab Antibody Response:

A total of 11 subjects in study C0524T09 tested positive for antibodies to golimumab. Ten of these 11 subjects had measurable serum golimumab concentrations through Week 24 and were included in the population PK analysis. The remaining subject who also tested positive did not have any measurable serum golimumab concentrations through Week 24 and the PK of golimumab in this subject could not be characterized. As such, this subject was not included in the population PK data set.

Figure 38 shows the EBE of CL/F in subjects with RA according to antibody-to-golimumab status (i.e., positive versus negative). Results of this analysis showed that subjects who tested positive with measurable golimumab levels had a 36% higher CL/F than subjects who did not. However, since relatively few (n = 10) subjects in this PK analysis population tested positive, the impact of antibody status may not be accurately quantified.



(Figure Note: IRP = antibody-to-golimumab status [ie, immune response positive].)

Figure 38. Empirical Bayesian Estimates of CL/F by Antibody-to-Golimumab Status: Final Model.

Other Concurrent Conditions:
The effects of several concurrent conditions (ie, hyperlipidemia, diabetes mellitus, and hypertension) as well as cigarette smoking status and use of alcohol were also assessed during the covariate analysis. In all, none of these baseline concurrent conditions had any significant effects on golimumab CL/F or V/F.

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Summary of PK parameters in three patient populations:

Table 7. Summary of typical population PK parameters in the three disease populations (RA, PsA, and AS).

Population PK Parameter Estimate (95% CI)[a]	RA	PsA	AS
CL/F (L/day)[b]	1.91 (1.80-2.03)	1.38 (1.30-1.47)	1.41 (1.31-1.51)
V/F (L)[b]	26.7 (24.5-28.7)	24.9 (22.7-26.9)	22.6 (20.7-24.4)
Ka (1/day)	0.668 (0.564-0.875)	0.908 (0.701-1.170)	1.010 (0.760-1.460)

[a]Typical population PK parameters estimated by NONMEM with the original final population PK dataset, and 95% confidence intervals calculated using 1,000 re-sampled and successfully converged bootstrapping runs are presented.
[b]Based on standardized weight of 70 kg

Reviewer's Analysis/Comments
The reviewer finds the population pharmacokinetic analysis conducted by the sponsor acceptable. The estimates of the base model for population PK were reproducible.

Labeling Statements
The following labeling statements are derived based on population pharmacokinetic analysis. Proposed labeling language is in "Arial" font. Suggested changes were tracked.

b(4)

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 10