

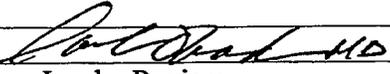
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 31, 2009
From	Sarah Okada, M.D. 
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125289/0
Supplement#	
Applicant	Centocor, Inc.
Date of Submission	June 25, 2008 (letter date June 24, 2008)
PDUFA Goal Date	April 24, 2009
Proprietary Name / Established (USAN) names	Simponi®/golimumab
Dosage forms / Strength	50 mg / pre-filled syringe (PFS) or PFS in autoinjector for subcutaneous (SC) injection
Proposed Indication(s)	1. Rheumatoid Arthritis 2. Psoriatic Arthritis 3. Ankylosing Spondylitis
Recommended:	Approval for all three proposed indications, with revisions to proposed labeling.

1. Introduction

BLA 125289 is the first marketing application for golimumab, a humanized monoclonal antibody (mAb) targeting Tumor Necrosis Factor- α (TNF α). The application contains data from 5 adequate and well-controlled studies in 3 rheumatologic indications: rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Three of the 5 golimumab pivotal trials were conducted in RA patients, one trial evaluated PsA patients, and one trial evaluated AS patients. Historically, the Agency has considered these three indications sufficiently closely related such that although at least two adequate and well-controlled trials are required in one of the three indications (typically, RA) that these data could then be used to support a single adequate and well-controlled trial conducted in each of the other indications. Therefore the number of studies per indication in this application is consistent with the number of studies required for approval of other TNF inhibitors for these indications.

If approved, golimumab would represent the fifth TNF inhibitor approved in the US, along with infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), and certolizumab (Cimzia®). As noted in Table 1, below, infliximab, etanercept, and adalimumab have already been approved for RA, PsA, and AS, with the first approvals dating back to 1998. Thus the focus of the review of BLA 125289 was not only to evaluate the efficacy and safety of golimumab as demonstrated in its clinical development program, but to assess whether there were any unusual or unexpected aspects of its efficacy and safety given the history of clinical experience with the other TNF inhibitors in the targeted indications.

Table 1: Summary of Currently Approved TNF Inhibitors

Summary of TNF Inhibitors Currently Approved in the U.S.				
TNF inhibitor	Molecule	Dose/Route	Indications	Year approved
Infliximab (Remicade®)	chimeric mAb	5 mg/kg IV, 0,2,6, then q 8 wks ¹	Crohn's Disease	1998
		3 mg/kg IV, 0,2,6, then q 8 wks ¹	Rheumatoid Arthritis	1999
		5 mg/kg IV 0,2,6, then q 6 wks	Ankylosing Spondylitis	2004
		5 mg/kg IV 0,2,6, then q 8 wks	Psoriatic Arthritis	2005
		5 mg/kg IV 0,2,6, then q 8 wks	Ulcerative Colitis	2005
		5 mg/kg IV 0,2,6, then q 8 wks	Pediatric Crohn's	2006
		5 mg/kg IV 0,2,6, then q 8 wks	Chronic Plaque Psoriasis	2006
Etanercept (Enbrel®)	TNF receptor fusion protein	50 mg SC once a wk	Rheumatoid Arthritis	1998
		or 25 mg twice a wk	Juvenile Rheumatoid Arthritis ²	1999
		JIA—0.8 mg/kg/wk, max 50 mg dose	Psoriatic Arthritis	2002
			Ankylosing Spondylitis	2003
		Chronic Plaque Psoriasis	2004	
Adalimumab (Humira®)	humanized mAb	40 mg SC q 2wks	Rheumatoid Arthritis	2002
		160 mg load (Crohn's)	Psoriatic Arthritis	2005
		80 mg load (Psoriasis)	Ankylosing Spondylitis	2006
		JIA <30 kg— 20 mg q 2 wks	Crohn's Disease	2007
			Chronic Plaque Psoriasis	2008
		Juvenile Idiopathic Arthritis ²	2008	
Certolizumab (Cimzia®)	Pegylated anti-TNF Fab fragment	400 mg SC at wks 2, 4, then q4wks	Crohn's Disease	2008

¹ Maintenance dose may be titrated to 10 mg/kg as clinically indicated

² Juvenile Rheumatoid Arthritis and Juvenile Idiopathic Arthritis are essentially the same population using different nomenclature systems

Sources: Drugs@FDA, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>, accessed 2-22-09, and approved labels accessed at company websites 2-22-09

2. Background

TNF α is a key proinflammatory cytokine which mediates a number of biological processes that can result in joint damage, including stimulation of bone resorption, inhibition of bone formation, and inhibition of the synthesis of proteoglycans. It additionally induces the production of other inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6), chemokines, and degradative enzymes such as matrix metalloproteinases. Although first detected as a protein that could induce tumor necrosis in 1960, it was isolated and thusly named in 1975 by Lloyd Old's laboratory group at Sloan-Kettering [Clark 2007]. In reality, the previously identified "necrotic" activity of Tumor Necrosis Factor appears to be due to TNF's effects in inducing apoptosis of proliferating endothelial cells, resulting in destruction of tumor microvasculature [Hundsberger 2008].

TNF inhibition has been previously demonstrated to be beneficial for the treatment of the three indications that are the subject of this BLA. RA is the most common inflammatory arthritis, affecting 2 million adults in the US (approximately 1% of the population), with onset between the ages of 30-55, mean affected age in the 50's, and female predominance (75%). The hallmark of RA is symmetric synovitis affecting the small joints of the hands and feet (metacarpal/metatarsal-phalangeal joints and wrists/ankles), which is often destructive and associated with erosions and joint space narrowing. Seventy to 75% of RA patients have

erosions within the first 3 years [Combe 2009]. Systemic inflammation is present, and extra-articular manifestations are uncommon, but can include interstitial lung disease, splenomegaly, pericarditis and vasculitis.

PsA is also an inflammatory arthritis, however differs from RA in prevalence (lower, at 0.3 to 1% of the population), demographics (approximately equal male:female ratio, slightly younger mean age of late 40's), and joints involved (asymmetric, tendency toward distal involvement, involvement of the spine, and involvement of the tendons as well as synovium—dactylitis and enthesitis). In 80-85% of cases, skin involvement with psoriasis has occurred previously or contemporaneously with the joint disease. Because of its tendency to involve the spine (occurring in up to 40% of PsA patients) and lack rheumatoid factor (RF), PsA is considered one of the seronegative spondyloarthropathies. Approximately 20% of PsA patients develop a destructive, disabling arthritis, and approximately 50% of patients with early PsA have evidence of erosions [Gladman 2005]. Outcome measures utilized for RA, such as the American College of Rheumatology (ACR) response criteria and Health Assessment Questionnaire Disability Index (HAQ-DI, or HAQ) have been validated for use in PsA as well, have been used successfully in previous clinical trials of PsA, and were used in the golimumab PsA trial.

In contrast to RA and PsA, the inflammatory changes of AS, another seronegative spondyloarthropathy, primarily involve the spine. The prevalence of AS is estimated to be 0.2 to 0.9% of the population, with 2:1 male:female ratio and disease onset in the 20's [Sieper 2009]. Transient arthritis of the peripheral joints may occur in 50% of patients, but only 25% of patients have persistent peripheral arthritis. When this occurs, the arthritis tends to be oligoarticular and asymmetric. Enthesitis is common in AS patients, often affecting the Achilles tendon or plantar fascia insertions. Dactylitis may also occur, but less commonly than with PsA. Sacroiliitis occurs early in 90% of cases and is most often bilateral. Extra-articular manifestations include anterior uveitis, which occurs in 25% of patients, and atrio-ventricular node conduction defects and aortic insufficiency, which occur in approximately 3-5% of patients with long-standing severe disease. Fifty percent of patients develop syndesmophytes, and fewer develop the full-blown ankylosis of the spine which gives the disease its name. Nonetheless, the disease is chronic, progressive, and can result in significant disability even in the absence of ankylosis. Because of its unique clinical features, a distinct set of outcome measures is required to measure treatment effects in AS. The Ankylosing Spondylitis Assessment Group (ASAS) criteria for improvement is a validated outcome measure that was used in the golimumab AS trial and will be described in further detail in the efficacy section of this review.

The Agency had several pre-submission regulatory interactions with the applicant regarding golimumab's clinical development program. The Agency's expectations regarding the number of trials needed for PsA and AS (one trial each, along with at least two trials in RA), the size of the safety database, various aspects of trial design, and necessary data for a change in formulation from liquid in vial (LIV) to pre-filled syringe (PFS) were discussed. For additional details, refer to Table 2.8 in the primary clinical review by Dr. Eric Brodsky. All issues were addressed in accordance with Agency guidance by the time of the BLA submission for golimumab.

3. CMC/Device

Primary CMC Reviewer: Kurt Brorson, Ph.D.

CMC Team Leader (Acting): David Frucht, M.D.

Much of the following section has been excerpted from Dr. Frucht's and Dr. Brorson's reviews.

- **General product quality considerations**

Golimumab (CNTO148, SIMPONI) is a human IgG1 κ monoclonal antibody directed against human tumor necrosis factor alpha (TNF α), derived using xenomouse technology. Xenomice have human immunoglobulin genes in place of mouse immunoglobulin genes; the mice are then immunized with the target of interest in order to raise human anti-target antibodies. The anti-TNF antibody that was selected for development, CNTO148, was then

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Golimumab has a β -pleated sheet structure and a carbohydrate structure that is typical of monoclonal antibodies (mAbs). The mass weight of golimumab is 150-151 kDa. Golimumab demonstrated a higher binding affinity and slower dissociation from TNF α in bioassays comparing it to infliximab, however this did not appear to translate into increased effects on clinical outcomes based on the 5 pivotal study results in the BLA (see section 7 below).

The mechanism of action for golimumab is to neutralize the activity of human TNF α via binding of soluble TNF α by golimumab, preventing this cytokine from binding to cell surface TNF receptors, and consequently preventing the initiation of downstream signaling cascades. Golimumab is also capable of binding to cell-membrane-bound TNF. In addition, the Fc region of the golimumab antibody functions to bind FcRn and Fc γ R1. Golimumab has been shown to be capable of binding complement and mediating complement dependent cytotoxicity (CDC) of mTNF^{hi} transfectomas. However, mTNF^{lo} cells (LPS-stimulated monocytes), which are more representative of leukocytes from patients with active inflammatory disease, are not susceptible to golimumab-mediated CDC.

The golimumab drug substance manufacturing process is based on Centocor's mAb platform, and has undergone several major variations, including one site change during Phase 2. These processes varied with respect to site, scale, cell line and unit operation, but generally improved the product throughout development. The final optimized process was based on design of experiment studies analyzing critical quality attributes, impurity clearance, viral clearance, and other attributes after varying key and critical unit operation parameters (e.g. buffer strengths, column flow rates, reaction times, etc.). Biochemical bridging studies were performed between the different process changes. Requalification of cell lines was performed after the cell line switch between phase 1 & 2. Product made between the various processes was determined to be functionally equivalent.

The drug substance is manufactured at Centocor B.V. in Leiden, the Netherlands. Drug Substance lot release testing included color of solution, identity by double radial immunodiffusion, capillary SDS (reduced and non-reduced), dual wavelength size exclusion-HPLC, capillary isoelectric focusing, bioactivity test, protein concentration, bioburden, endotoxin (LAL), and pH. Release specifications were based on trend analysis and

calculations of tolerance intervals; the specifications are deemed appropriate by FDA CMC reviewers. Centocor has proposed a 36-month expiry for Drug Substance, based on real-time data and extrapolation from trend analysis. To support 36-month expiry, Centocor has provided acceptable data for five lots stored at -40° C for 24 months, and four lots stored at -40° C for 18 months. In addition, they have provided acceptable data for four lots stored at -18° C for 12 months. Trending analysis and confidence intervals calculated from this analysis indicate that the Drug Substance will remain within acceptable criteria for at least 36 months; the FDA CMC team concurs that the proposed 36-month expiry is acceptable.

Golimumab is provided in 1 mL pre-filled syringes that are assembled with a Centocor Autoinjector or _____ intended for single use. For the clinical trials, golimumab was supplied in two dosage formats (100 mg/1 mL and 50 mg/0.5 mL). Each dosage format contains 100 mg/mL golimumab, and compendial grade excipients of 4.1% (w/v) sorbitol, 5.6 mM l-histidine, and 0.015% polysorbate-80 dissolved in Water for Injection. Of note, the 100 mg dosage format being used in the ongoing clinical studies is not being proposed for marketing in this BLA. Drug product manufacture (syringe fill) occurs at _____ Assembly of the pre-filled syringe into an autoinjector or _____ as well as labeling and packaging, occurs at Cilag AG, Schaffhausen, Switzerland. Labeling and/or packaging of the assembled devices takes place at Ortho-McNeil Pharmaceuticals, Inc., Raritan, NJ. Drug product lot release tests included color of solution, appearance of primary container, identity by double radial immunodiffusion, capillary sodium dodecyl sulfate (reduced and non-reduced), dual wavelength size exclusion-HPLC, capillary isoelectric focusing, bioactivity, protein concentration, sterility, endotoxin (LAL), pH, visible particulate matter, visible translucent particles, sub-visible particulates, turbidity, osmolality, extractable volume, glidability, piston release force, piston travel force, expelled volume (autoinjector), and force to actuate (autoinjector). These lot release tests were reviewed and determined to be acceptable. See section 11, below for additional details regarding the testing and qualification of the proposed devices.

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The recommended storage temperature for golimumab drug product is 2-8° C. The applicant proposes a drug product expiry of 24 months, and provided real-time stability data from three lots of drug product in prefilled syringes supporting this expiration dating. Trend analysis and confidence intervals calculated from this analysis indicate that the drug product will remain within acceptance criteria for at least 36 months, thus the proposed expiry of 24 months was determined by FDA CMC reviewers to be acceptable.

- **Facilities review/inspection**

Two facilities underwent pre-approval inspections: (1) Centocor BV (Drug Substance manufacture; Leiden, The Netherlands; January 28- February 3, 2009) and (2) _____ February 4-6, 2009). A major CMC-related inspectional issue was the high percentage of syringes/vials (clinical drug product used for the clinical trials) with process-related particles present. Centocor partially addressed this issue before the inspection by improving visual inspection procedures at contract fill sites. Additional follow-up regarding this issue includes improvements to the

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investigation procedures (i.e., implementation of Acceptable Quality Level standards) and a likely pre-approval inspection when Cilag AG is reviewed under a prior approval supplement for commissioning as a pre-filled syringe fill site. Another major inspectional issue was the occurrence of false-positive results for adventitious virus testing of unprocessed bulk harvest at the [REDACTED] facility (see below). Inspections for other sites (drug product fill, cell bank testing, autoinjector assembly site) have been waived, as they are frequently inspected by the Office of Regulatory Affairs (ORA). b(4)

- **Other notable issues (resolved or outstanding)**

On October 6, 2008, Centocor notified FDA of adventitious virus detection from numerous cell culture harvest samples from golimumab and another monoclonal antibody product manufactured by Centocor. These assays were performed by the [REDACTED] testing facility, and when replicated at two additional contract testing laboratories, the test articles were negative. [REDACTED] was inspected, and the root cause of these positive results was judged to be a non-optimized assay, which was not initially evident due to insufficient attention to the negative control. An extensive investigation, including a more vigilant review of the negative controls, revealed that the positive "foci" were cell clumping due to matrix effects and a non-optimized assay format. The clumping was also present in the negative controls, providing evidence that these results were false positives. This observation, in conjunction with an extensive investigation by Centocor using more advanced techniques that failed to detect any virus in the test articles, indicated that the results had been false positives. The [REDACTED] facility inspection (February 4-6, 2009) revealed that various aspects of the assay that were sub-optimal, including overgrowth of the indicator cells after 14 days, resulted in false positive readings. b(4)

The current assay for detection of adventitious virus contamination in the unprocessed bulk harvest performed at [REDACTED] is a sub-optimal legacy assay dating from the 1980's and has an unacceptable percentage of false positives, which may be attributable to subtleties in assay performance. As a temporary safety measure, testing has been transferred to a second contract testing organization, [REDACTED], where this assay has not been susceptible to matrix effects. As a permanent solution, FDA CMC reviewers recommend a postmarketing commitment to optimize the existing assay or develop an improved assay for detecting adventitious virus contamination in the unprocessed bulk harvest. They otherwise consider the data in the application adequate to support approval of the BLA. b(4)

4. Nonclinical Pharmacology/Toxicology

Primary Pharmacology/Toxicology Reviewer: Gary Bond, Ph.D.

Pharmacology/Toxicology Supervisor: Adam Wasserman, Ph.D.

Much of this section was excerpted from Dr. Bond's and Dr. Wasserman's reviews.

- **General nonclinical pharmacology/toxicology considerations**

Golimumab demonstrated binding and target neutralization of monkey TNF α but did not demonstrate activity against TNF- α from mouse, rat, rabbit or dog. Therefore, all pivotal

nonclinical data necessary for product approval was developed using the cynomolgus monkey as the nonclinical model.

The pivotal nonclinical studies in monkeys for golimumab include two 6-month chronic toxicology studies (SC and IV), an embryofetal development study (SC), and a pre- and post-natal development study (SC). Safety pharmacology endpoints were incorporated into intravenous (IV) and subcutaneous (SC) repeated dose toxicology studies conducted with golimumab in cynomolgus monkeys that also included neonatal assessments as part of the SC prenatal and postnatal reproductive toxicology study in monkeys. The safety pharmacology endpoints incorporated into these studies included measures of heart rate, blood pressure and electrocardiograms to assess cardiovascular safety, respiratory rate to assess respiratory safety and body temperature and daily clinical cage side observations to evaluate central nervous system safety. No mortality or golimumab-related clinical signs of toxicity were observed during the dosing and post-dosing periods; neither was there any treatment-related effect observed in the safety pharmacology assessments, immunotoxicity evaluations, macroscopic, histopathologic, or immunohistopathologic evaluations. The No Observed Adverse Effect Levels (NOAELs) in the pivotal nonclinical studies were the highest dose tested in those studies. Anticipated pharmacological actions of TNF α inhibition and minimal local tolerance/injection site effects were observed at these NOAELs and were considered clinically monitorable and reversible. Results of the reproductive toxicology studies were negative (see section on reproductive and developmental toxicology below). Specific assessments of local tolerance/injection site effects in monkeys were also conducted—single and repeated SC injections in monkeys with golimumab at doses up to 50 mg/kg were well tolerated at the injection site with minimal local irritation being observed.

Of note, some impairment of the T-cell Dependent Antibody Response (TDAR) was observed with the IV route and was characterized by fewer monkeys generating measurable IgG upon exposure to a super-antigen (Keyhole Limpet Hemocyanin, KLH) when compared to vehicle-treated controls (see notable issues section below). As anti-KLH IgM response was less affected than IgG this suggests a possible treatment-related interference with isotype class switching. This was not observed in monkeys administered golimumab via the SC route – the proposed clinical route – and toxicokinetic comparison of the two studies revealed a two-fold higher AUC exposure with the IV route which may explain this differential response.

Additional supportive studies conducted with a surrogate anti-mouse TNF α mAb (cV1q) were also submitted and included chronic repeat dose toxicology studies and reproductive toxicology studies (fertility and early implantation, embryofetal development, and a pre- and post-natal development) in mice. These studies were identical to those submitted in support of Centocor's BLA 103,772 (Remicade®, infliximab) for the same indications. These studies also indicated acceptable safety margins for reproductive toxicity and for chronic toxicity with suggestion that preneoplastic/neoplastic changes did not occur after chronic dosing.

- **Carcinogenicity**

Genotoxicity tests have not been conducted with golimumab. The range and type of genotoxicity studies routinely conducted for small-molecule drugs have not been routinely

required for biopharmaceutical antibodies and is consistent with ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

Carcinogenicity tests have not been conducted with golimumab. The carcinogenic potential of golimumab cannot be evaluated in standard 2-year bioassays in rodents because golimumab does not neutralize rodent TNF α . Thus the carcinogenic potential of golimumab was evaluated by attempting to understand the mechanism of action of the therapeutic mAbs for the TNF α class of drugs and via data on malignancy from the golimumab clinical program and available information from the clinical experience with other approved TNF inhibitors. Preneoplastic/neoplastic lesions were assessed as part of chronic studies in mice and monkeys with no indications of any treatment-related preneoplastic/neoplastic lesions.

- **Reproductive and developmental toxicology**

Reproductive toxicology studies have not been conducted with golimumab in the traditional rodent and rabbit nonclinical models, as golimumab does not neutralize rodent or rabbit TNF α . Golimumab has been tested for embryofetal and prenatal and postnatal effects in an appropriate nonclinical test species, cynomolgus monkeys. As part of BLA 103,772 (infliximab), the effects of anti-TNF α treatment on reproductive toxicology were assessed in the mouse using cV1q, an analogous anti-mouse TNF α mAb that allowed for the evaluation of fertility and early embryonic development, embryofetal development, and prenatal and postnatal development.

In the embryofetal monkey study, pregnant female cynomolgus monkeys were dosed by the subcutaneous route twice weekly from days 20 to 51 of gestation at doses of 0, 25, or 50 mg/kg golimumab. High dose group dams gained 8% less weight than controls while low dose dams gained comparable weight as controls. No effects were observed on fetal viability, fetal weight, placental weight, external measurements, organ weights, or fetal external, placental, viscera or skeletal findings in either the male or female fetuses.

In the prenatal and postnatal monkey study, pregnant female cynomolgus monkeys were dosed by the subcutaneous route twice weekly from day 50 of gestation to day 33 after delivery at doses of 0, 25, or 50 mg/kg golimumab. Nothing remarkable was noted for maternal animals or neonates, including immunological and immunohistochemical assessments.

Fertility and early embryonic development, embryofetal, and prenatal and postnatal studies were conducted in CD-1 mice at doses of 10 or 40 mg/kg using an analogous anti-mouse TNF α mAb (cV1q), with dosing by the intravenous route. These studies showed parental and offspring exposure to cV1q but no treatment-related effects. In the prenatal and postnatal study, a reduction in the pregnancy rate of F1 mice was considered of none to minimal toxicological relevance as the pregnancy rate (76%) was only slightly below the historical rate (83 to 100%) and another study with cV1q in mice revealed no maternal or developmental toxicity up to 40 mg/kg dosage. In addition, no treatment-related effects were observed in the F2 generation. Based on the immunological parameters evaluated, administration of cV1q to male and female CD-1 mice did not adversely affect the immune function in F1 mice, with the possible exception of a decrease in humoral immune response at the 40 mg/kg dosage level,

which is an anticipated pharmacological effect. Otherwise, intravenous administration of cVlg at dosages of up to 40 mg/kg/day in CD-1 mice did not result in developmental toxicity.

- **Other notable issues (resolved or outstanding)**

According to the pharmacology/toxicology review, there were no significant issues raised by the nonclinical data and there were large safety margins above the clinical therapeutic exposure in humans. The pharmacology/toxicology team has determined that the nonclinical data in this submission support approval of the BLA. They did not identify additional nonclinical studies to be recommended as post-marketing commitments or requirements. However, notable issues identified included:

1) Impairment of TDAR with supratherapeutic IV doses of golimumab in cynomolgus monkeys. This concern was allayed by a lack of similar impairment observed with SC dosing in monkeys, and by clinical data in humans demonstrating unimpaired responses to immunization at therapeutic doses of golimumab.

2) Disagreement with the applicant's interpretation of fetal:maternal plasma exposure results from the monkey embryofetal development study. The applicant obtained fetal umbilical vein blood at the time of cesarean section to estimate fetal exposure and compare values with maternal blood levels. Based on these values, they posit that fetal serum concentrations were roughly 50% of maternal concentrations. While technically true at the time of C-section, this is not accurately reflective of fetal exposure throughout the dosing period since, similar to humans, mAbs do not pass the placental barrier in monkeys until late in the 2nd trimester equivalent. Therefore the 50% fetal exposure claim would not be operative during the period of organogenesis (and maternal dosing). The pharmacology/toxicology team plans to handle this via revisions to the proposed pertinent language in the package insert.

3) Anti-product antibody (APA) evaluations. It is difficult to interpret the limited toxicity observed in the nonclinical studies without an understanding of whether neutralizing antibodies were present in the animals that may have obscured treatment-related toxicity. Unfortunately, the assay utilized by the applicant for these studies was a "bridging ELISA" format, which is particularly prone to interference by significant levels of circulating drug product. Thus the APA evaluations submitted are of limited utility. These concerns were mitigated by the observation that the few animals identified as APA-positive had significantly lower levels of drug product exposure which may suggest alterations in drug product clearance occur upon significant APA response or, alternatively, that lower levels of plasma exposure allow APA to be detected. Additionally, separate validation assays, which were performed to demonstrate drug product quantification in toxicokinetic samples, indicated that a positive anti-product antibody response interferes with golimumab measurement. Therefore, the high levels of golimumab detected in toxicokinetic assays appear to indicate that even if APA were present, these did not interfere with detection of the drug product and therefore sufficient exposure to active drug product occurred in the nonclinical toxicity studies.

4) Unusual toxicokinetics in pregnant monkeys. An unexplained 5-fold exposure difference was observed when comparing non-pregnant with pregnant monkeys administered the same

dose regimen and level. This may have been due in part to differences in intrinsic factors, as monkeys in the embryofetal study were older and heavier than female monkeys in the other chronic studies, resulting in a 2-fold higher total dose (dosing was based on weight). Nonetheless, despite the 5-fold higher exposure, pregnant monkeys did not demonstrate unusual toxicities.

5. Clinical Pharmacology/Biopharmaceutics

Primary clinical pharmacology/pharmacometrics reviewer: Lei Zhang, Ph.D.

Clinical Pharmacology Team Leader: Suresh Doddapaneni, Ph.D.

Secondary pharmacometrics review: Atul Bhattaram, Ph.D.

Pharmacometrics Team Leader: Yaning Wang, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

Three SC pharmacokinetic (PK) studies were conducted in healthy subjects (single dose, 50 or 100 mg, total n=237). Two PK studies (IV—0.1 mg/kg to 10 mg/kg, n=23; SC—0.3 mg/kg to 3 mg/kg, n=17) were conducted in RA patients. PK data were also obtained from the clinical trials in the targeted indications for Population-PK (POP-PK) analyses. As shown in Table 2, below, in the dedicated PK studies with frequent sampling, RA patients appeared to have lower clearance and longer half-life of golimumab compared to healthy subjects. However, this difference was not apparent in POP-PK analyses from the clinical trials, where the clearance and half life of golimumab appeared to be similar to data observed from the healthy subject PK studies. Of note, use of concomitant methotrexate (MTX) appeared to be associated with lower clearance and longer half-life of golimumab; these values were closer to the values observed in healthy subjects. This may be due to a lower rate of anti-product antibody formation with concomitant use of MTX, as anti-product antibodies were generally associated with higher clearance and lower serum golimumab concentrations in the 5 Phase 3 studies.

Table 2: Golimumab PK parameters in Healthy Subjects and Patients with RA, PsA or AS

Golimumab PK Parameters for Healthy Subjects and Patients with RA, PsA, or AS				
Population	CL/F (e.g. 70kg subject) from POP-PK analysis	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 patients	+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 patients	19.7 mL/day/kg	12.5 days	-	-
AS patients	20.1 mL/day/kg	11.1 days	-	-

*Results of dense sampling in dedicated PK studies

Source: Table 2.2.8.1 of Dr. Zhang's review

Based on a cross-study comparison of mean AUC_{inf} data from IV and SC administration at dose levels of 0.3 mg/kg and 3.0 mg/kg, the absolute bioavailability of golimumab after SC administration is estimated to be between 44 and 58%.

- **Drug-drug interactions**

Antibodies and other large proteins are not metabolized by cytochrome P450 enzymes (CYP). For this reason, historically, in vitro or in vivo drug-drug interaction assessments have not been required for therapeutic biologics. Nonetheless, recent data suggest that cytokines themselves may affect expression of CYP, and thus modulation of these cytokines via therapeutic biologics may affect the metabolism of drugs that are CYP substrates (see notable issues section below). Although clinically relevant interactions of this nature have not been reported with the other approved TNF inhibitors, the clinical pharmacology team is recommending a Phase 4 study to further assess for this possibility.

Commonly used concomitant medications in the rheumatic diseases, including disease-modifying-antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids, were evaluated for effects on golimumab PK via POP-PK analyses. As noted above, concomitant MTX decreased apparent clearance of golimumab in RA patients, who otherwise demonstrated higher clearance compared to healthy subjects. Covariate analysis did not demonstrate a similar effect in PsA and AS patients. No other concomitant medications appeared to affect golimumab PK. Golimumab has not been studied with concomitant biologic DMARDs.

- **Exposure-Response relationships**

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. As shown in Table 3 below, no consistent exposure-response relationships were noted in increasing doses from 50 mg every 4 weeks to 50 mg every 2 weeks to 100 mg every 4 weeks. Although 100 mg every 2 weeks produced the highest proportion of ACR20 responders, similar increases were not noted for ACR50 and ACR70 responses.

Table 3: Exposure-Responses in RA Dose-Finding Study C0524T02

Exposures and ACR Responses in RA Dose-Finding Study C0524T02					
	placebo	CNTO 148			
		50 mg q4 wks	50 mg q2 wks	100 mg q4 wks	100 mg q2 wks
subjects, n	35	35	34	34	34
mean steady-state trough, µg/mL	-	0.48	1.16	1.20	3.37
mean steady-state peak, µg/mL	-	1.71	3.82	4.08	7.78
ACR 20 responders, n (%)	13 (37)	21 (60)	17 (50)	19 (56)	27 (79)
ACR 50 responders, n (%)	2 (6)	13 (37)	8 (24)	10 (29)	11 (32)
ACR 70 responders, n (%)	0 (0)	3 (9)	5 (15)	6 (18)	3 (9)

Source: Section 2.2.5 and Table 2.2.5.1 from Dr. Zhang's review

Based on the efficacy and safety results in this trial, the applicant selected the 50 mg q4 week and 100 mg q4 week dosing regimens for the Phase 3 trials in RA, PsA and AS. As discussed

in sections 7 and 8 below, efficacy results in the Phase 3 trials suggested no additional benefit of the 100 mg dosing regimen over the 50 mg dosing regimen, and the 50 mg dosing regimen appeared to have a more favorable safety profile; for example, a lower exposure-adjusted incidence of deaths and serious infections.

b(4)

- **Intrinsic factors/special populations**

Although no dedicated PK studies were conducted to assess intrinsic factors or special populations, 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. Patients with heavier weight tended to have higher clearance; however this is unlikely to have influenced clinical efficacy or safety parameters, as there is no evidence of an exposure-response relationship between the doses studied in the Phase 3 trials. Age and race (mainly Caucasian vs. Asian) did not appear to impact on the PK of golimumab in adult RA, PsA, and AS patients. In RA and PsA patients, there was no difference in PK parameters between genders. In the AS study, gender was a significant covariate based on covariate analysis and females showed higher apparent clearance. However, again this difference is unlikely to have clinical import due to the lack of correlation with exposure and response.

No clinical studies of golimumab have yet been conducted in pediatric populations and no formal PK studies were conducted in subjects with renal or hepatic impairment.

- **Product development and comparability among product lots and presentations**

During the clinical development of golimumab, clinical material from 2 cell lines _____ and 2 different formulations (lyophilized and liquid) 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. This same liquid formulation in a prefilled syringe (PFS) was used in several healthy volunteer Phase 1 studies and in all Phase 3 studies after Week 24. The final product will be a liquid formulation of golimumab in a PFS fitted with the _____, or the same PFS in an autoinjector.

b(4)

A biochemical equivalency study was performed to demonstrate that product made by the two cell lines _____ was equivalent. A nonclinical, single SC dose PK comparison study of the material produced by the 2 cell lines _____ showed that golimumab produced from the 2 different cell lines had similar PK profiles in cynomolgus monkeys (Study P-2002-008). The liquid and lyophilized formulations were found to be comparable in a nonclinical pharmacokinetic comparability study (Study P-2005-003).

b(4)

The comparability of the PFS with the Phase 3 LIV presentation and the PFS in autoinjector presentations were assessed 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 (i.e., 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) fell within Agency standards of 80% to 125%; however, the 90% CI for Cmax was 96% to 127%, which fell slightly outside the upper limit of the 80% to 125% range. Although the data did not show bioequivalence with Cmax, the difference is small and not considered clinically significant. The applicant is proposing a 50 mg dose, and a 100 mg dose was studied in clinical trials with an acceptable safety profile. Therefore, a slightly higher Cmax with autoinjector would not pose a safety concern.

- **Thorough QT study or other QT assessment**

Because therapeutic proteins and antibodies are large molecules that are not anticipated to be able to exert effects on the cardiac conduction system, thorough QT/QTc studies were neither required of nor conducted with golimumab. Pre- and post-treatment ECGs were obtained in Phase 1 placebo-controlled studies (2 in RA and 2 in healthy subjects) and no significant ECG abnormalities were noted.

- **Other notable issues (resolved or outstanding)**

The clinical pharmacology/biopharmaceutics team has determined that the data in this submission support approval of the BLA from their perspective.

Because cytokines such as TNF α have been shown to downregulate the expression of cytochrome P450 enzymes (CYP) in humans, it is possible that inhibition of TNF with golimumab treatment may reverse the effect of the cytokine on CYP substrates, resulting in a normalization of CYP regulation and potential drug interaction with P450 substrate drugs upon initiation or discontinuation of golimumab treatment. This may have clinical implications for P450 substrates with a narrow therapeutic index, primarily via loss of efficacy as CYP activity normalizes and metabolism of the P450 substrate drugs increases. Thus, the clinical pharmacology team recommends a Phase 4 commitment for *in vitro* or *in vivo* drug interaction studies to assess the potential effect of golimumab on Cytochrome P450 substrate drugs.

While I concur that DDI studies may provide useful information, clinically problematic interactions have not been reported in the extensive clinical experience with TNF inhibitors to date, making it difficult to conclude that such studies are necessary to enhance the safe use of golimumab. I performed a search of PubMed on 3-24-09, using a combination of the terms "TNF," "TNF inhibitor," and "TNF blocker" with potentially interacting drugs of interest, such as tramadol (which must be metabolized to active compound, and therefore might be subject to increased effects with the putative interaction from initiation of TNF inhibitor therapy), warfarin, theophylline, and oral contraceptives. No cases of clinical drug interactions

were reported. Similarly, a PubMed search on the terms “TNF” and “drug interactions” yielded no cases of clinical drug interactions with cytochrome P450 substrates.

I then performed a search of the FDA Adverse Event Reporting System (AERS) Datamart on 3-25-09 using the 4 approved TNF inhibitors (adalimumab, certolizumab, etanercept, infliximab) and 6 representative potentially interacting drugs (losartan and tramadol, which must be metabolized by CYP enzymes to become bioactive, and warfarin, theophylline, ethinyl estradiol and phenytoin, as examples of drugs for which change in concentrations would be clinically important). One case of a possible drug-drug interaction was identified. This case (report number 3970925) was reported in August 2002, in which a 27 year old female who was taking Loestrin as an oral contraceptive (for approximately 8-9 months) was diagnosed as pregnant after approximately 4 infusions of infliximab 5 mg/kg. The patient was a smoker and was taking concomitant mesalamine as well. The temporal relationship of the start of infliximab treatment and the pregnancy could be consistent with a drug-drug interaction. No suspicious cases were identified for adalimumab, certolizumab, or etanercept.

After, I relayed the results of the above AERS search to Drs. Zhang and Doddapaneni, Dr. Zhang requested an additional search of AERS for interactions with statins and cyclosporine. I conducted this search on March 26 and March 27. Although there were well over 100 adverse event reports in which a TNF inhibitor and statins or cyclosporine were mentioned, all cases were adverse effects known to be associated with one drug or the other (for example combinations with cyclosporine where patients experienced infection or malignancy). I did not find any cases where the described adverse event would likely represent the anticipated drug interaction (i.e., due to increased metabolism of the statin or cyclosporine).

Approximately 20% of patients with RA receive TNF inhibitor treatment [Cush, 2005], which translates into over 400,000 patients in the US; and TNF inhibitors have been approved for 11 years. Although it is possible that TNF inhibitor/CYP substrate interactions may exist, the extensive clinical experience to date would suggest that these interactions, for the most part, have not been clinically significant or problematic, although a single suspicious case was identified. Thus, I believe the recommended drug interaction studies are more appropriate as postmarketing commitments rather than as post-marketing requirements under the Food and Drug Administration Amendments Act (FDAAA). After internal discussions with Dr. Zhang and Dr. Doddapaneni, and their discussions with OCP upper management, they concur that the recommended DDI studies may be requested as postmarketing commitments.

6. Clinical Microbiology

- Not applicable

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Eric Brodsky, M.D.

Primary Statistical Reviewer for RA Trials: Jonathan Norton, Ph.D.

Primary Statistical Reviewer for PsA and AS Trials: Joan Buenconsejo, Ph.D.

Statistical Team Leader: Dionne Price, Ph.D.

7.1 Indication: RA

The applicant submitted the results of 24-week controlled data from 3 ongoing (planned for 5-years total) pivotal trials in RA:

- Study C0524T05 evaluated the effect of monthly SC golimumab treatment in 637 MTX naïve early RA patients, randomized 1:1:1:1 to golimumab 100 mg monotherapy, golimumab 50 mg and golimumab 100 mg in combination with MTX, and MTX monotherapy. MTX was optimized to a dose of 20 mg once weekly by Week 20 for all but the golimumab monotherapy group. The primary endpoint for the study was the proportion of ACR50 responders at Week 24. Major secondary endpoints included ACR20 responses at Week 24, and ACR50 responses at Week 24 in the subset of patients with elevated C-reactive protein (CRP) at baseline.
- Study C0524T06 evaluated the effect of monthly SC golimumab treatment in 444 RA patients with inadequate response to MTX ≥ 15 mg/weekly, comparing golimumab 100 mg monotherapy (n=133), golimumab 50 mg (n=89) and golimumab 100 mg (n=89) in combination with stable doses of background MTX, and background MTX alone (n=133). The primary endpoint for this study was the proportion of ACR20 responders at Week 14. If the study was successful at demonstrating statistical significance for the primary endpoint, a “co-primary” endpoint of improvement from baseline in HAQ-DI at Week 24 was to be tested. Major secondary endpoints included ACR20 responses at Week 24, Disease Activity Score-28 (DAS28) at Week 14, and improvement from baseline in HAQ-DI at Week 14.
- Study C0524T11 evaluated the effect of monthly SC golimumab treatment in 461 RA patients with inadequate response to DMARDs and a history of previous TNF inhibitor use. Patients were randomized to placebo add-on (n=155), golimumab 50 mg add-on (n=153), or golimumab 100 mg add-on (n=153) to background DMARDs. The primary endpoint for this study was the proportion of ACR20 responders at Week 14. Major secondary endpoints included ACR50 at Week 14, DAS28 at Week 14, ACR20 at Week 24, and improvement from baseline in HAQ-DI at Week 24.

7.1.1 Claim: Reducing Signs and Symptoms

Table 2 below summarizes the primary endpoint results in the golimumab RA trials, which were all based on the ACR response criteria. These criteria represent a composite endpoint which includes 7 core set variables: swollen joint count, tender joint count, physician’s assessment of disease activity, patient’s assessment of disease activity, patient’s assessment of pain, patient’s assessment of physical function (using validated indices such as HAQ-DI), and levels of acute phase reactants (either c-reactive protein or erythrocyte sedimentation rate). An ACR20 response is defined as at least 20% improvement in both tender joint count and swollen joint count and at least 20% improvement in 3 of the 5 other core set variables. ACR50 and 70 responses are calculated similarly using 50% and 70% improvement, respectively.

As discussed in the statistical review by Dr. Jon Norton, the applicant used a gatekeeping sequence to address multiplicity across doses, which combined the results of the golimumab + MTX (or DMARD) groups to first test vs. the control group. If the null hypothesis was rejected for that comparison, then individual doses would be tested.

For Studies T06 and T11, the combined golimumab 50 and 100 mg group demonstrated superiority vs. the control group for the primary endpoint of the proportion of ACR20 responders at Week 14 ($p < 0.001$ in both studies). With the exception of the golimumab monotherapy arm in Study T06, the individual golimumab dose groups in the two studies also demonstrated higher rates of ACR20 responses that were statistically significant. Results with respect to ACR20 responses at Week 24, and ACR50 and ACR70 responses at Week 14 and Week 24, were consistent with the primary endpoint results.

In contrast to Study T06 and T11, the primary endpoint for Study T05 was the proportion of ACR50 responders at Week 24, and Study T05 failed to demonstrate the superiority of the combined golimumab groups vs. MTX (p -value 0.53), despite numerically higher response rates in the golimumab groups. Had the applicant chosen ACR20 responses as the primary endpoint in this study, they might have succeeded in demonstrating statistically significant superiority, since the golimumab + MTX groups each had 62% ACR20 responders vs. 49% ACR20 responders in the MTX monotherapy group; a slightly greater treatment effect-size in favor of golimumab (see Table 6.6 from Dr. Brodsky's review for ACR response criteria secondary endpoint results). Regardless, previous experience with MTX and other TNF inhibitors in the MTX-naïve early RA population has also supported the conclusion that TNF inhibitors are not superior to optimized MTX in this population, so the results of Study T05 are not unexpected.

Table 4: Primary Endpoint Results in the Golimumab RA Trials

Primary Endpoint Results in the Golimumab RA Trials					
Study T05 (MTX naïve)	MTX + pbo (n=160)	Golimumab 100 monox (n=159)	Golimumab + MTX		
			50 mg (n=159)	100 mg (n=159)	Combined (n=318)
ACR50, Wk 24	29%	33%	40%	37%	38%
p-value vs MTX	-	0.521	0.042	0.177	0.053
Study T06 (MTX-inadequate)	MTX + pbo (n=133)	Golimumab 100 monox (n=133)	Golimumab + MTX		
			50 mg (n=89)	100 mg (n=89)	Combined (n=178)
ACR20, Wk 14	33%	44%	55%	56%	56%
p-value vs MTX	-	0.059	0.001	<0.001	<0.001
Study T11 (Prior TNF use)	DMARDs + pbo (n=155)		Golimumab +/- DMARDs		
			50 mg (n=153)	100 mg (n=153)	Combined (n=306)
ACR20, Wk 14	18%		35%	38%	37%
p-value vs MTX	-		<0.001	<0.001	<0.001

Source: Tables 13, 16, and 17 of CSR

Study T05 and Study T06 both included a 100 mg golimumab monotherapy arm, and in both studies this treatment arm failed to achieve statistically significant differences despite

numerically higher responses compared to the control groups. [REDACTED] the applicant is not seeking approval of golimumab monotherapy treatment for the RA indication. Also of note, the results of the three RA trials suggest no additional benefit of 100 mg golimumab compared to 50 mg, in terms of ACR responses. Accordingly, the applicant is seeking approval of only the 50 mg dose in this BLA.

b(4)

7.1.2 Claim: Improving physical function

Based on previous FDA guidance (from 2005) and the currently published RA Guidance Document (ca. 1999), the applicant did not seek the claim of improving physical function based on the 24-week data submitted in this BLA. The basis of the requirement of 2-year data for this claim, as discussed in the RA Guidance, was the initial belief that impairment in physical function in RA was due to joint damage, and that a significant amount of time would be necessary to observe improvements that were related to reduction in joint damage. However, experience with other TNF inhibitors has demonstrated that improvement in physical function can actually be observed in a short period of time, and that in fact much of the functional impairment that RA patients experience is due to inflammation in, rather than mechanical damage of, the joints. Thus it is reasonable to consider granting the claim based on physical function endpoint results (HAQ-DI, in this case) at similar timepoints as the signs and symptoms endpoints, i.e., 12 or 24 weeks. Although long-term impairment in physical function due to joint damage is not captured utilizing short-term physical function endpoints, the joint damage may be assessed via long-term effects on radiographic endpoints, [REDACTED]

b(4)

The applicant identified improvement in HAQ-DI from baseline to Week 24 as a “co-primary” endpoint (actually, a second primary endpoint, to be tested after the ACR Response Criteria primary endpoint) in Study T06 and as a major secondary endpoint in Study T11. Analyses of these two studies form the basis of the data in this submission that could support this claim. Interim HAQ-DI results from baseline to Week 24 were also provided from Study T05, however in this study, change in HAQ-DI from baseline to Week 52 was designated as a major secondary endpoint. As shown in Table 3 below, golimumab treatment was associated with a greater mean change from baseline to Week 24 in HAQ-DI in Studies T06 and T11, and the difference was statistically significant. Additionally, a higher proportion of patients in the golimumab treatment groups achieved an improvement of ≥ 0.25 u, a minimally clinically important difference in HAQ-DI in RA patients. In the early RA patient population, the magnitude of improvement in HAQ-DI was high in all treatment arms, including the optimized MTX control arm, but was numerically higher in the golimumab treatment arms, consistent with results in the other golimumab RA studies.

Table 5: HAQ-DI Results in the Golimumab RA Trials

HAQ-DI Results in the Golimumab RA Trials					
Study T05 (MTX naïve)	MTX	Golimumab	Golimumab + MTX		
	+ pbo (n=160)	100 monox (n=159)	50 mg (n=159)	100 mg (n=159)	Combined (n=318)
mean change, baseline to Wk 24	-0.52	-0.57	-0.62	-0.72	
proportion with improvement ≥ 0.25 u					
observed data only	67%	68%	73%	79%	
nonresponder imputation	63%	61%	68%	73%	
Study T06 (MTX-inadequate)	MTX	Golimumab	Golimumab + MTX		
	+ pbo (n=133)	100 monox (n=133)	50 mg (n=89)	100 mg (n=89)	Combined (n=178)
mean change, baseline to Wk 24	-0.13	-0.24	-0.47	-0.45	-0.46
p-value vs. MTX control	-	0.24	<0.001	<0.001	<0.001
proportion with improvement ≥ 0.25 u					
observed data only	39%	45%	68%	72%	70%
nonresponder imputation	35%	42%	65%	64%	
Study T11 (Prior TNF use)	DMARDs		Golimumab +/- DMARDs		
	+ pbo (n=155)		50 mg (n=153)	100 mg (n=153)	Combined (n=306)
mean change, baseline to Wk 24	-0.05		-0.25	-0.28	-0.27
p-value vs. DMARD control	-		<0.001	<0.001	<0.001
proportion with improvement ≥ 0.25 u					
observed data only	35%		51%	54%	
nonresponder imputation	28%		44%	49%	

Source: Module 2.7.3 Tables 4 and 9, Table 18 of Dr. Norton's review, Table 6.7 of Dr. Brodsky's review

7.2 Indication: PsA

The applicant is seeking approval for golimumab 50 mg SC once monthly, with or without concomitant DMARDs for the indication of PsA, based on 24-week results from Study C0524T08. This study enrolled and randomized 405 patients with active PsA to continue on their background therapy with placebo added-on (n=113) vs. golimumab 50 mg (n=146) or golimumab 100 mg (n=146) added-on for the first period of 24 weeks. Week 24 to 52 is a blinded active treatment period, in which placebo patients are crossed over to active treatment with golimumab 50 mg although the blind is maintained. Beginning at Week 52, all patients are treated open-label for an extension period to Week 268.

The primary endpoint was the proportion of ACR20 responders in the combined golimumab group at Week 14 compared to placebo. The applicant also designated change from baseline to Week 24 in radiographic scores as a "co-primary" endpoint (again, this is actually a second primary endpoint, to be tested after the ACR Response Criteria primary endpoint) for the study, _____

Major secondary endpoints included the proportion of ACR20 responders at Week 24, proportion of patients achieving 75% improvement in the Psoriasis Area and Severity Index (PASI), mean change from baseline to Week 24 in HAQ-DI score, and change from baseline to Week 14 in the Physical Component Summary (PCS) of the Short Form Questionnaire (SF-36).

b(4)

7.2.1 Claim: Reducing Signs and Symptoms

Table 4, below, summarizes the primary endpoint results for Study T08. Treatment with golimumab resulted in a higher proportion of responders at Week 14 compared to placebo (48% vs. 9%). The primary endpoint results were analyzed for subgroups by concomitant use of MTX (See Table 8 of the review by FDA statistician Dr. Joan Buenconsejo). Results were similar for both subgroups and were consistent with the primary endpoint results. Results of ACR20 at Week 24 and for ACR50 and ACR70 responses at Week 14 and Week 24 were also consistent with the primary endpoint results (See Table 6.18 of Dr. Brodsky's review) and support the conclusion that golimumab is effective for the treatment of PsA.

Table 6: Primary Endpoint Results in the Golimumab PsA Trial

Primary Endpoint Results in the Golimumab PsA Trial				
Study T08	Placebo +/- DMARDs (n=113)	Golimumab +/- DMARDs		
		50 mg (n=146)	100 mg (n=146)	Combined (n=292)
ACR20, Wk 14	9%	51%	45%	48%
p-value vs control group	-	<0.0001	<0.0001	<0.0001

Source: Table 2 of the T08 CSR

7.2.2 Claim: Improving Physical Function

For assessing improvement in physical function in PsA, the HAQ-DI has also been validated for use in this population, with an identified MCID of ≥ 0.3 units. The results of the applicant's pre-specified major secondary endpoint of mean change from baseline to Week 24 in HAQ-DI confirm that golimumab treatment results in greater mean improvement compared to treatment with placebo +/- DMARDs, and the difference is statistically significant.

Table 7: Week 24 HAQ-DI Results in the Golimumab PsA Trial

Week 24 HAQ-DI Results in the Golimumab PsA Trial				
Study T08	Placebo +/- DMARDs (n=113)	Golimumab +/- DMARDs		
		50 mg (n=146)	100 mg (n=146)	Combined (n=292)
Mean change from baseline to Week 24	-0.01	-0.33	-0.39	-0.36
p-value vs control group	-	<0.001	<0.001	<0.001
proportion with improvement ≥ 0.30 u				
LOCF	23%	43%	52%	48%
observed data only	22%	43%	52%	48%
BOCF	21%	41%	51%	46%

Source: Table 6, Module 2.7.3 of the T08 CSR and Table 13 of Dr. Buenconsejo's review

The proportion of patients achieving \geq MCID levels of improvement was also higher in the golimumab treatment groups. The applicant provided an analysis using last-observation-carried-forward (LOCF) for missing data; the differences between the golimumab groups and the control group were statistically significant. These differences remained statistically significant whether observed data or baseline-observation-carried-forward (BOCF) imputation were used.

7.3 Indication: AS

The applicant is seeking approval for golimumab 50 mg SC once monthly, with or without concomitant DMARDs for the indication of AS, based on 24-week results from Study C0524T09. This study enrolled and randomized 356 patients with active AS to continue on their background therapy with placebo added-on (n=78) vs. golimumab 50 mg (n=138) or golimumab 100 mg (n=140) added-on for the first period of 24 weeks. Week 24 to 104 is a blinded active treatment period, in which placebo patients are crossed over to active treatment with golimumab 50 mg although the blind is maintained. Beginning at Week 104, all patients are treated open-label for an extension period to Week 268.

The primary endpoint was the proportion of patients achieving ASessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. The primary analysis was the comparison of the combined golimumab treatment groups vs. the control group. An ASAS 20 response is defined as a relative improvement of $\geq 20\%$ from baseline and an absolute improvement of ≥ 1 cm on 0 to 10 cm scales in at least 3 of 4 domains: patient global assessment, patient pain, inflammation-related back stiffness (which is the mean of assessments 5 and 6 on the Bath AS Disease Activity Index, BASDAI), and physical function using the Bath AS Functional Index (BASFI). In conjunction with these improvements, the 4th remaining domain must not demonstrate worsening (defined as $\geq 20\%$ relative worsening or absolute worsening of ≥ 1 cm on 0 to 10 cm scale). The ASAS response criteria have been validated and have been successfully used in other trials of TNF inhibitors in AS. Major secondary endpoints for the study included the proportion of patients achieving an ASAS 20 response at Week 24, the change from baseline to Week 14 in BASFI, and the change from baseline to Week 14 in the Bath Ankylosing Spondylitis Metrology Index (BASMI), which is a composite of 5 measures of hip and spine mobility. For additional details of the AS efficacy measures, refer to Table 6.33 of Dr. Brodsky's review.

7.3.1 Claim: Reducing Signs and Symptoms

The primary endpoint for Study T09 was the proportion of patients achieving ASAS 20 responses in the combined golimumab group vs. the control group. As shown in Table 6 below, 60% of patients in the combined golimumab group achieved ASAS 20 responses compared to 22% of patients in the placebo +/- DMARD control group, and this difference was statistically significant. A statistically significant difference in favor of golimumab treatment was noted in the individual golimumab 50 mg and 100 mg groups as well. Consistent with results in the RA and PsA trials, there did not appear to be a difference between the 50 mg and 100 mg golimumab groups with respect to ASAS responses.

Table 8: Primary Endpoint Results in the Golimumab AS Trial

Primary Endpoint Results in the Golimumab AS Trial				
Study T09	Placebo +/- DMARDs (n=78)	Golimumab +/- DMARDs		
		50 mg (n=138)	100 mg (n=140)	Combined (n=278)
ASAS 20, Wk 14	22%	59%	60%	60%
p-value vs control group	-	<0.0001	<0.0001	<0.0001

Source: Table 2 of Module 2.7.3 of the T09 CSR and Table 1 of Dr. Buenconsejo's review

No agents currently approved for AS have yet been approved for additional claims pertaining to physical function and mobility, although BASFI and BASMI, respectively, are among the indices reportedly validated for assessing these outcomes [Zochling and Braun, 2005]. Based on studies with other TNF inhibitors, TNF inhibition appears to have salutary effects on function and MRI evidence of spinal inflammation [Braun and Sieper, 2008]. However, the same cannot be said for TNF inhibition and effects on syndesmophyte formation and ankylosis. It is not clear whether the lack of evidence of effect is due to the long duration over which these structural effects occur (and that therefore changes may not be captured in the timeframe of typical clinical trials), or whether this is due to pathophysiologic processes in play that may not be particularly susceptible to TNF inhibition. Treatment with TNF inhibitors has had variable effects on measurements of mobility in clinical trials. Treatment with golimumab in Study T09 resulted in greater improvement in the BASFI compared to placebo, but did not result in improvement in the BASMI.

- **Discussion of both the statistical review and the clinical efficacy review with attention to any disagreements and how they were addressed**

There were no disagreements among the clinical and statistical review team members regarding the efficacy results in the 5 Phase 3 studies. Studies T06 and T11 in RA, Study T08 in PsA, and Study T09 in AS were successful in rejecting the null hypothesis for their respective primary endpoints. Study T05 in methotrexate-naïve early RA patients failed to reject the null hypothesis that there is no difference between golimumab treatment and optimized methotrexate treatment, as a control. However the results in T05 were not unexpected since optimized methotrexate is known to be a highly efficacious treatment for RA.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

The FDA statistical team for the BLA raised concerns regarding the applicant's use of "biased-coin" randomization. As per Dr. Norton's explanation, "this class of methods seeks to minimize the imbalance of treatment assignments across stratification factors by identifying the treatment assignment for a particular subject that would yield the best balance given prior assignments, then giving that treatment the highest probability of selection. While biased-coin randomization yields the desirable result of better balance, it can potentially invalidate the results of conventional statistical tests which assume completely random assignment." In order to address this concern, the Agency requested re-randomization testing for all 5 pivotal studies. For details on what this testing entailed, refer to Dr. Norton's statistical review. The results of re-randomization testing supported the results of the conventional statistical tests.

Therefore the statistical team concurred with the clinical review team that the efficacy results in this submission were adequate to support approval for the three indications sought.

8. Safety

- **Safety Overview**

In the entire safety database of 13 completed studies of golimumab, 2894 patients received at least one dose of golimumab. In the 5 Phase 3 trials, 2057 patients were exposed to golimumab treatment for at least 24 weeks, with 1768 of these patients having exposure for at least 52 weeks at the time of the 120-day safety update data cut-off of June 2, 2008. Thus the size of the safety database in this BLA conforms with Agency expectations, as discussed during golimumab's clinical development, and are consistent with the safety databases required of the other approved TNF inhibitors.

The major safety findings in the RA, PsA and AS trials were consistent with previous clinical experience with other TNF inhibitors. The exposure-adjusted incidence of death was highest in the golimumab 100 mg q 4 week treatment group. The 14 deaths observed in the Phase 3 trials to date were reported due to malignancy (3 cases), sepsis (2 cases), cardiac etiologies (3 cases), and isolated other events. Notably, a single fatality due to acute liver failure and bleeding complications due to liver biopsy was reported in a young female RA patient ultimately diagnosed with autoimmune hepatitis (see discussion on liver enzyme abnormalities below).

The exposure-adjusted incidence of serious infectious events (SIE) in the control groups of the Phase 3 studies was higher than in either of the golimumab treatment groups, and exceeded published background rates in RA patients taking non-biologic DMARDs, making relative comparison to this group problematic. However exposure-adjusted incidence in the golimumab treatment groups (5 SIE per 100 patient-years for 100 mg, 3.4 SIE per 100 patient-years for 50 mg) was consistent with rates reported for other TNF inhibitors. Consistent with the labeled warnings of the approved TNF inhibitors, 7 cases of tuberculosis, 2 cases of histoplasmosis, and 1 case of coccidioidomycosis were observed in the golimumab clinical development program. Single cases of opportunistic infection with listeria, legionella, and pneumocystis were also observed, as were single cases of hepatitis B infection and herpes zoster.

The exposure-adjusted incidence of overall malignancy was similar to controls in the golimumab groups and was consistent with expected background rates in the general population. However, an increased incidence of lymphoma (standardized incidence ratio of 3.8) was noted; RA patients are reported to have an increased background risk for lymphoma. Of note, golimumab treatment was clearly associated with an increased incidence of malignancy in a Phase 2 asthma trial, in which patients were randomized equally to treatment with placebo or one of three doses of golimumab: 50 mg, 100 mg, and 200 mg. Eight patients receiving golimumab were diagnosed with malignancies in this trial (including 2 patients with

non-melanoma skin cancer) compared to no malignancies in the placebo control group. Five of these patients were in the 200 mg golimumab treatment group, 2 patients were in the 100 mg group, and 1 patient was in the 50 mg group, suggesting a dose-relationship. While the relationship of TNF inhibition to malignancy has yet to be conclusively established, TNF was initially identified as an agent that induced “tumor necrosis,” as discussed in section 2 above. This is now postulated to be due to its effects in inducing apoptosis of proliferating endothelial cells, resulting in destruction of tumor microvasculature. Nonetheless, plausible mechanisms therefore exist for inhibition of TNF to interfere with potentially protective endogenous processes and allow for unfettered growth of incipient malignancies.

Overall the safety profile of golimumab appears to be consistent with the approved TNF inhibitors and no unique safety concerns were identified in this submission. The four currently approved TNF inhibitors have Medication Guides addressing the risks of malignancy and serious infections. On September 4, 2008, DAARP issued a letter informing the sponsors of the currently marketed tumor necrosis factor (TNF) blockers (including Centocor, the sponsor of infliximab and golimumab) that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to address the risk of unrecognized histoplasmosis and other invasive fungal infections associated with TNF inhibitor use. The letters specified that the REMS consist of a Medication Guide, a Communication Plan, and a timetable for the submission of assessments of the REMS. Specifically, sponsors were advised that the Communication Plan must include a DHCP letter and other printed or web-based materials to inform healthcare providers about the occurrence of unrecognized histoplasmosis and other invasive fungal infections. The applicant has submitted a REMS proposal consisting of a Med Guide, Communication Plan, and timetable of assessments. The applicant’s REMS proposal has been preliminarily been reviewed by the Division of Risk Management (DRISK), and additional details regarding the Communication Plan materials have been requested from the applicant. DRISK review of the proposed Med Guide is completed. No substantive content issues were identified, but extensive revisions were proposed to improve clarity and consistency, and will be relayed to the applicant.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

There were a total of 14 deaths in the ongoing Phase 3 trials through the data cut-off date of June 2, 2008. Exposure-adjusted incidence of deaths was slightly higher among patients treated with the 100 mg q 4 week dosing regimen, with 0.45 deaths per 100 patient-years compared to 0.39 deaths per 100 patient-years in the control group. Exposure-adjusted incidence of deaths in the dose proposed for approval (50 mg q 4 weeks) was lower than that of controls, at 0.34 deaths per 100 patient-years. These rates are well below published background rates of death in RA patient cohorts, which is estimated to be 2.4 to 2.5 deaths per 100 patient-years. As noted above, the attributed causes of deaths in the golimumab trials were of the type that would be expected in the patient population or with immunosuppressive therapy.

SAEs

Overall, serious adverse events (SAEs) were uncommon, occurring in 5-6% of patients in each treatment group, including controls. The exposure-adjusted incidence of SAEs was highest in the control group, with 17 SAE per 100 patient-years. Approximately 12 SAE per 100 patient-years were observed in the golimumab 50 mg and 100 mg dose groups. Infections were the most commonly reported types of SAE in all groups. Refer to Table 7.3.6 in Dr. Brodsky's review for additional details.

DAEs

Discontinuations due to adverse events (DAEs) were also uncommon, occurring in 3-4% of patients in each treatment group, including controls. The exposure-adjusted incidence of DAEs was highest in the control group, at approximately 10 DAE per 100 patient-years, compared to 6 and 7 DAE per 100 patient-years in the golimumab 50 mg and 100 mg treatment groups, respectively. Patients in the golimumab groups more commonly discontinued due to infections or transaminase elevations whereas patients in the control group more commonly discontinued due to arthritis flares and headache. Refer to Table 7.3.7 in Dr. Brodsky's review for additional details.

Common AEs

Common adverse events occurred in 70% of patients in the control groups and 75% of patients in each of the golimumab treatment groups. The types of adverse events observed were typical and consistent among the treatment groups; the top five diagnoses consisted of upper respiratory tract infections, nasopharyngitis, nausea, headache, and fatigue.

Laboratory Abnormalities

Transaminase elevations have been reported in association with the approved TNF inhibitors, and golimumab is no exception. Among patients with normal baseline ALT in the Phase 3 trials, approximately 25-30% of golimumab-treated patients experienced at least one ALT elevation up to 3 x upper limit of normal (ULN) during the study, compared to 20% of patients in the control groups (who were typically on DMARDs +/- NSAIDs). The incidence of ALT elevations from 3 to 8 x ULN was low (4%) and equivalent in the golimumab and control groups. Marked ALT elevations above 8 x ULN were uncommon (less than 1% in each treatment group), but was highest with the golimumab 100 mg dose (5 of 885 patients with normal baseline ALT, 0.6%). A total of 6 patients experienced hepatobiliary laboratory abnormalities that fit Hy's criteria of transaminase elevations >3 x ULN and total bilirubin > 2 x ULN in the golimumab clinical development program (13 studies); 4 patients were on golimumab and 2 patients were in the control groups. However all cases were confounded by either concomitant hepatotoxins, such as NSAIDs, MTX, alcohol, acetaminophen or isoniazid, or other likely etiologies, such as viral hepatitis or immune-mediated liver disease.

Isolated events of acute liver failure and hepatic necrosis have been reported with approved TNF inhibitors (e.g. infliximab, adalimumab), and again, golimumab is no exception. These cases have often been confounded by the presence of concomitant hepatotoxins, or the coexistence of other potential etiologies such as viral hepatitis or immune-mediated liver disease. This was the case with the 24-year old Korean female RA patient who died of acute liver failure (more accurately, after experiencing severe bleeding complications from her liver

biopsy) during Study T06. This patient had a history of immune-mediated thyroid disease and a prior history of hospitalization for evaluation of elevated liver enzymes 8 months prior to receiving golimumab. However, at the time of entry, she met study inclusion criteria which included liver enzyme elevations no greater than 1.5 x ULN. Early in the study, on Day 55, the patient was noted to have transaminase elevations of 5 x ULN. She was taking suspect herbal medications, which were discontinued, with resolution of transaminase elevations by Day 68. Her terminal course began on Day — when she was hospitalized with 7 days of fever, chills, cough, nausea, vomiting, left upper quadrant pain, hepatosplenomegaly and elevated hepatobiliary parameters. Viral serologies were negative. Liver biopsy was performed to further evaluate and the patient experienced massive post-procedural bleeding requiring multiple transfusions and an attempted embolization of the hepatic artery. The patient died within —. Liver biopsy showed mild to moderate hepatocellular injury, mild sinusoidal dilation and congestion, and portal fibrosis. b(5)

Mechanistically, TNF α exerts pleiotropic effects in the liver, as both a mediator of hepatotoxicity and in maintaining functional liver mass by driving hepatocyte proliferation and regeneration [Schwabe 2006]. Because of these dual roles, there is no clearly anticipated net effect of TNF inhibition on the liver. Experience with other approved TNF inhibitors suggests that liver enzyme abnormalities are not unexpected with TNF inhibitor treatment; however there does not appear to be a significant risk for treatment-related clinically-manifested hepatotoxicity in the absence of concomitant hepatotoxic insults. The clinical trial experience with golimumab suggests a similar situation.

All four approved TNF inhibitors are labeled with warnings regarding cytopenias, however cytopenias have also been reported with the underlying disease and other DMARDs. In the golimumab Phase 3 trials, approximately 1% of patients in each treatment group, including controls, experienced anemia. Approximately 2% of patients experienced low WBC or neutrophils in both golimumab dose groups compared to 0.5% of patients in the control group. Hematologic abnormalities tended to be transient and were not associated with clinical adverse events. There was no consistent pattern of laboratory abnormalities in serum chemistries or lipid profiles associated with golimumab treatment.

- **Immunogenicity, allergenicity, and injection site reactions**

Overall, immunogenicity to SC golimumab exposure was low, and consistent with levels observed with other approved SC TNF inhibitor formulations. As expected, concomitant methotrexate use did appear to lower the incidence of human-anti-human-antibody (HAHA) formation. Among patients in both the 50 mg and 100 mg dose groups, 2% of patients on MTX developed anti-golimumab HAHA compared to 7% of golimumab-treated patients who were not on MTX. Because of the small numbers of patients testing HAHA positive, it is difficult to draw definitive conclusions, however in general these patients did not appear to experience lack of response or loss of efficacy and did not appear to be at increased risk for allergic reactions or injection site reactions. There was no difference in immunogenicity between the LIV formulation and the to-be-marketed PFS formulation (1% HAHA positivity for either formulation in the bioequivalence study).

There were no cases of anaphylactic or anaphylactoid reactions in the Phase 3 trials. The number of patients experiencing urticaria, hypersensitivity, or rash was low overall. Golimumab treatment appeared to be associated with a slightly higher incidence of urticaria (0.5 to 0.6% in the golimumab groups vs. 0.3% of controls). Rash occurred in approximately 3% of patients in the control group and the golimumab 50 mg group and was slightly higher in the golimumab 100 mg group (3.6%). Injection site reactions were also infrequent, but appeared to increase with the higher dose of golimumab; 3% of patients in the control group experienced injection site reactions vs. 7% with golimumab 50 mg and 9% with golimumab 100 mg.

- **Special safety concerns**

Autoimmunity

Contemporaneous additional autoimmune diagnoses are uncommon but not unexpected in patients with autoimmune disease. However, all four approved TNF inhibitors have labeled warnings or precautions regarding the possible association of TNF inhibitor use and the formation of new autoantibodies and/or new autoimmune diagnoses because there are invariably a few cases in every clinical development program in the rheumatic diseases.

In the golimumab clinical development program, 1 patient developed new onset cutaneous lupus erythematosus, 2 patients developed vasculitis, and 6 patients developed pustular psoriasis. In all cases, patients were on golimumab, however definitive conclusions cannot be drawn because the time period patients were on placebo add-on control was so much less than the total exposure time period for golimumab. Nonetheless, there does appear to be a plausible association with TNF inhibitor treatment and pustular psoriasis. This form of psoriasis is otherwise extremely uncommon and refractory to treatment, however when reported in association with TNF inhibitor treatment, often responds to discontinuation of the TNF inhibitor. This is in contrast to spontaneously occurring psoriasis, which commonly responds to TNF inhibitor treatment. The association with TNF inhibitors and pustular psoriasis is the subject of an ongoing Agency safety review, with probable resultant labeling changes. At present, there have been approximately 69 serious cases of new-onset psoriasis reported to the FDA postmarketing adverse events database in association with TNF inhibitor use.

Response to Immunization

An expected consequence of immunosuppression is a decrease in desirable immune response activities as well, such as response to immunization. Therefore the Agency has historically required sponsors of biologic immunosuppressives intended for the treatment of rheumatic disease to assess the impact of treatment on immunization responses. Multiple immunization studies have been conducted with the approved TNF inhibitors and there does not appear to be a significant decrement in immunization responses associated with TNF inhibitor treatment. This is also true for golimumab, based on immunization results for patients in the Phase 3 trials. Patients receiving either dose of golimumab appeared to respond to similar degrees as patients on placebo. Approximately 90% of patients achieved at least 2-fold increases in anti-pneumococcal antibody titers after pneumococcal vaccination. Response was slightly l

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Other labeled events of interest

The approved TNF inhibitor labels also contain warnings and/or precautions regarding congestive heart failure (CHF) and demyelinating disorders. The warning regarding CHF is based on exploratory clinical trials of TNF inhibitors for the treatment CHF, in which TNF inhibitor treatment was demonstrated to unexpectedly worsen CHF and increase mortality. Patients with a history of CHF, including medically controlled CHF, were excluded from participation in the golimumab clinical trials. In the golimumab clinical development program, comprised of 13 studies, 4 patients developed CHF. Three of the patients were in golimumab treatment groups, and 1 patient was receiving placebo. These patients were discontinued from their respective trials.

Only one patient developed symptoms of a possible demyelinating disorder: a 53 year old female RA patient with a history intermittent right lower extremity hypoaesthesia and paresthesias, who enrolled in the golimumab trial and was randomized to the 100 mg treatment group. At 2 timepoints during the trial (Day 22 and Day 133) the patient experienced exacerbation of her symptoms, associated with diplopia. After her first exacerbation, the patient was evaluated for possible MS, including MRI and CSF analysis. The MRI had nonspecific white matter changes and a small enhancing C2 spinal cord lesion was noted. CSF evaluation was negative. After the second exacerbation, the patient was discontinued from the study. Neurosurgical and neurological follow up were ongoing at the time of the last safety submission to the BLA. Repeat MRI and CSF evaluations were consistent with the initial tests; no definitive diagnosis has yet been made.

- **Discussion of primary reviewer's comments and conclusions**

Overall, Dr. Brodsky has concluded that the safety profile of golimumab in the proposed indications is consistent with the safety profiles of approved TNF inhibitors and I concur. The applicant has proposed a label that closely reflects the approved TNF inhibitor labels with respect to safety concerns, and proposes a boxed warning regarding the risk of serious infections, especially TB and invasive fungal infections, and warnings regarding serious infections, malignancies, hepatitis B reactivation, demyelinating disorders, and CHF. Dr. Brodsky and I concur that this is appropriate.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

Not applicable.

- **Discussion of notable safety issues (resolved or outstanding).**

No safety issues unique to golimumab have been identified.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this BLA, as golimumab represents the fifth TNF inhibitor in class and no unique or controversial issues were identified from the data in this submission.

10. Pediatrics

- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

Studies have not yet been conducted for golimumab treatment in pediatric patients. Polyarticular juvenile idiopathic arthritis (PJIA) is considered to be the pediatric equivalent of adult RA. Therefore, in accordance with the Pediatric Research Equity Act (PREA) of 2007, studies in PJIA are mandated. With this submission, Centocor requests a deferral for pediatric patients age 2-16 with PJIA because studies of golimumab in adult RA are completed and are ready for approval. This request has historically been granted for other therapeutic biologics, and should also be granted for golimumab, because it is ethically desirable to have adequate safety experience in adults before proceeding with extensive studies in pediatric patients. Centocor has requested a partial waiver for pediatric patients ages 0-2 with PJIA, since these studies would be highly impracticable because PJIA is extremely rare in this age group. This, too, has been historically granted, and should be granted for golimumab.

Centocor's proposed pediatric plan for PJIA includes

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Centocor plans to submit a pediatric study protocol for their proposed PK/safety/efficacy trial in the third or fourth quarter of 2009, with study initiation anticipated in the first quarter of 2010, and with submission of the final study report in 2013. While this is acceptable, an argument could be made that a PK/safety study in PJIA patients would be adequate.

The juvenile equivalents of PsA and AS are extremely rare, because pediatric patients with juvenile idiopathic arthritis do not typically develop sufficient distinguishing features of PsA or AS for specific diagnoses to be made during childhood. Therefore the Agency has historically granted waivers for pediatric studies in these two indications because studies would be highly impracticable.

These proposals were discussed with the Agency's Pediatric Review Committee (PeRC) on March 11, 2009. The PeRC concurred with the partial waiver for PJIA patients ages 0 to <2 years, the deferral for PJIA patients ages 2 to 16 years, and full waivers for the PsA and AS indications. They also stated they would find _____ acceptable to address the PREA requirement for studies in PJIA.

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11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):**

No problems were identified warranting invocation of the AIP.

- **Exclusivity or patent issues of concern**

Not applicable.

- **Financial disclosures**

Financial disclosures were reviewed and determined to be acceptable. Information was provided by the applicant on 8 investigators who had received past payments from Centocor or had significant equity interest in Johnson and Johnson, the parent company of Centocor. These investigators enrolled few patients and results would not have affected the overall trial outcomes. For further details, refer to section 3.3 in Dr. Brodsky's review.

- **Other GCP issues**

The applicant certified that they conducted all trials in this submission in compliance with good clinical practice (GCP) guidelines. No issues were identified that would counter this assertion.

- **DSI audits**

DSI reviewer, Good Clinical Practice Branch 1: Susan Liebenhaut, M.D.

DSI branch chief, Good Clinical Practice Branch 1: Constance Lewin, M.D., M.P.H.

No sites were identified as requiring an inspection "for-cause," e.g., due to irregularities in efficacy or safety results, or financial reasons. Of the approximately 190 sites world wide, no single site comprised more than 5 to 9% of the total study population for a given trial, thus no single site was identified that would alter the overall study results. The proportion of US patients in the studies ranged from 16 to 58%. Two sites were selected for routine audits; these two sites were selected because they represented the highest enrolling US sites. Two protocols were evaluated (C0524T08 and C0524T11) at each site. The applicant's records at their own facilities in Malvern Pennsylvania were also evaluated. The Division of Scientific Investigation (DSI) found no data integrity or study conduct issues.

- **Other consults**

CDRH consultation from Pandu Soprey, Ph.D., through Anthony Watson, Branch Chief, General Hospital Device Branch:

The golimumab formulated bulk is shipped to _____

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_____ Two PFS presentations are manufactured: a 50 mg/syringe dose (0.5 mL nominal fill volume) and a 100 mg/syringe dose (1.0 mL nominal fill volume). The golimumab PFS are then shipped to Cilag AG in Schaffhausen Switzerland for assembly into _____ or the Smartject® Autoinjector.

The [redacted] needle guard is a commercially available product and has been cleared by the United States (US) FDA for use as an accessory to a pre-filled glass syringe through the 510(k) premarket applications [redacted], as an accessory to a PFS. The needle guard is not in contact with the liquid drug during storage or use. The [redacted] is comprised of a spring loaded needle guard subassembly and a dedicated stopper rod (handle). During the assembly process the rod is threaded into the golimumab PFS stopper and the PFS is assembled with the needle guard subassembly.

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The Centocor Smartject[®] Autoinjector is very similar to marketed autoinjectors that have been cleared as Class II devices by CDRH. It uses a spring-powered mechanism to insert a hypodermic needle attached to a syringe through the skin to inject the drug at a predetermined depth in the subcutaneous tissue. The autoinjector performs all three phases of the injection process with a single push-button operation: needle insertion, complete drug injection, and needle withdrawal. A safety interlock sleeve prevents actuation until the autoinjector is pressed against the skin with moderate force. The injection depth is approximately 7.5 mm. The autoinjector delivers either a 0.5 mL or 1.0 mL dose depending on the fill volume of the syringe. The time from button actuation to needle retraction is less than or equal to 15 seconds. These parameters are similar to those used for manual injection for this same route of administration.

The Centocor Autoinjector has not been previously approved for marketing in the US or any international markets, but has been used in the golimumab clinical development program, and was specifically evaluated in the following studies:

- Protocol C0999D01, a Phase 1, randomized cross-over study to evaluate the safety and tolerability of placebo subcutaneously administered at 3 different injection sites using an investigational autoinjector device or a PFS;
- Protocol 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;
- Protocol C0999D02, an open-label randomized validation study to establish that the design, functionality, and ergonomic features of the Autoinjector conform to defined user needs and intended use for self-administration by subjects with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, or Psoriasis.
- A Simulated Use Study with health care professionals and patients who routinely administer subcutaneous medications. In this study, 65 evaluators were each instructed to actuate eight devices into an injection training pad. A total of 520 consecutive actuations were completed, simulating important clinical variables. The study tested the 1.0 mL version of the Autoinjector, which is identical to the 0.5 mL version except for a longer latch actuator and spacer. There were no failures, defined as either a needlestick injury or a significant problem with safety feature(s) that could lead to an injury), among the 520 actuations.
- A Self-Injection Study, which was a validation study of the Centocor Autoinjector in the target population. Sixty-eight subjects were enrolled (35 with RA, PsA or AS, and 33 with psoriasis). At least 15 subjects with RA or PsA were required to have impaired

hand function, and at least 15 were required to have had prior or current experience with SC self-administration. Each subject self-administered a total of two SC injections of placebo with the autoinjector (one in the abdomen and one in the thigh). One hundred percent of subjects were able to complete the injections with the first or second attempt in at least one of the injection sites regardless of diagnostic group or subgroup strata. These results supported the suitability of the device for the intended population.

CDRH review of the in-line checks performed during the assembly process, the in-process controls, and the release tests determined that testing encompassed full functional performance testing of the Centocor autoinjector as a finished medical device and ensured compliance with specifications, which were also determined to be acceptable. Refer to the CDRH consultative review for additional details.

12. Labeling

- **Proprietary name**

The applicant proposed a proprietary name of Simponi®. The Division of Drug Marketing, Advertising, and Communications (DDMAC) and the Division of Medication Errors Prevention and Analysis (DMEPA) were consulted and determined the name Simponi to be acceptable. The review team concurred with this assessment. DDMAC initially objected to use of the

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DDMAC then withdrew their objection.

- **Important issues raised by DDMAC and DMEPA**

DMEPA reviewer/TL (acting): Carlos Mena-Grillasca, RPh

DDMAC reviewer: Michael Sauers

DRISK reviewer: Sharon Mills, BSN, RN

DDMAC provided numerous comments for the package insert and Med Guide which has been taken into account by the review team during labeling discussions. These comments were primarily refinements and no major or unresolved issues have been identified.

- **Physician labeling**

The proposed package insert overall conformed to Physician's Labeling Rule (PLR) requirements and was patterned on approved TNF inhibitor labels with respect to content. Most of the changes to the proposed safety portion of the label will be refinements, and the review team does not have substantive disagreement with the proposed label in terms of content. However, in the clinical studies section of the label, the applicant has proposed a wide array of _____ for inclusion which will be removed.

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- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

There were no major issues or areas of disagreement with respect to the recommendations made by DDMAC, DMEPA, and DRISK reviewers.

- **Carton and immediate container labels (if problems are noted):**

DMEPA review of the carton and container labeling identified 16 refinements/clarifications to the proposed carton and container labeling. These comments will be relayed to the applicant for incorporation.

- **Patient labeling/Medication guide**

The applicant submitted a proposed MedGuide that largely conformed to the Cimzia MedGuide in format and to all four approved TNF inhibitor MedGuides in content. In general, the proposed MedGuide adequately addressed the known safety concerns associated with TNF inhibitor treatment, to include serious infections (including TB and invasive fungal infections) and malignancy. However, the Division of Risk Management (DRISK) consultant, Sharon Mills, recommended a large number of helpful clarifications and edits to the MedGuide. These recommendations were incorporated into the proposed MedGuide and DRISK comments will be relayed to the applicant.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

Recommend approval for RA, PsA and AS with revisions to the proposed label.

- **Risk Benefit Assessment**

Overall, the efficacy and safety profile of golimumab in the 5 pivotal trials in RA, PsA and AS was consistent with that observed with the other TNF inhibitors approved for these indications. No findings unique to golimumab were observed in the clinical development program.

In 2 of 3 pivotal RA studies in patients with previous inadequate response to MTX and in patients with a previous history of TNF inhibitor use, add-on treatment with golimumab was superior to add-on treatment with placebo with respect to the primary endpoint of the proportion of ACR20 responders at Week 14, with a treatment effect size of approximately 20% more responders in the golimumab groups compared to the control groups. In the third RA study, conducted in MTX-naïve early RA patients, treatment with golimumab was not superior to treatment with optimized MTX with respect to the primary endpoint of ACR50 responders at Week 24. However the failure to achieve a statistically significant difference was likely due to the efficacy of the comparator treatment rather than lack of treatment effect of golimumab, as response rates were high in all treatment arms. There were markedly higher

response rates in the golimumab groups of the PsA and AS trials compared to the control groups of those trials, with approximately 40% more patients achieving the primary endpoints of ACR20 or ASAS20 responses, respectively, at Week 14.

Similar to the approved TNF inhibitors, treatment with golimumab was associated with a higher exposure-adjusted incidence of deaths and serious infections. The types of deaths and serious infections observed were consistent with those previously observed in other TNF inhibitor trials or in the postmarketing period. Seven cases of tuberculosis, 2 cases of histoplasmosis and 1 case of coccidioidomycosis were among the serious infections reported with golimumab treatment. The exposure-adjusted incidence of overall malignancy was similar to controls in the golimumab groups; however, an increased incidence of lymphoma (standardized incidence ratio of 3.8) was noted. In a one-year Phase 2 study of 50, 100, and 200 mg golimumab for the treatment of asthma, 8 malignancies occurred in the golimumab treatment groups (increasing in a dose-related fashion) versus none in the placebo group, suggesting a deleterious effect resulting from TNF inhibition in this population.

As with other TNF inhibitors, the risk:benefit profile of golimumab treatment is generally favorable for the serious rheumatic conditions of RA, PsA and AS. The types of risks observed in the clinical development program are consistent with those observed in the clinical experience with other TNF inhibitors to date, and should be handled similarly. The recent (September 2008) requirement for sponsors of TNF inhibitors to have a REMS with a communication plan and medication guide should apply to golimumab as well.

- **Recommendation for Postmarketing Risk Management Activities**

As required of the sponsors of the 4 currently approved TNF inhibitors (see section 8 safety overview), a REMS consisting of a Medication Guide, Communication Plan, and timetable of assessments will be required for golimumab. The applicant has in fact submitted a REMS proposal consisting of a Med Guide, Communication Plan, and timetable of assessments. The applicant's REMS proposal has been preliminarily reviewed by the Division of Risk Management (DRISK), and additional details regarding the Communication Plan materials have been requested from the applicant. These details were recently submitted and are under review. DRISK review of the proposed Med Guide has been completed, and revisions will be relayed to the applicant for incorporation.

- **Recommendation for other Postmarketing Study Commitments**

1. PREA-required study in PJIA patients age 2-16. Recommend granting deferral of the study (PeRC concurs), with final report submission in December 2013.

2. Postmarketing Study Requirements under FDAAA: none

3. Postmarketing Commitments:

- 1) The current assay for detection of adventitious virus contamination in the unprocessed bulk harvest performed at is a sub-optimal legacy assay dating from the 1980's

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and has an unacceptable percentage of false positives. Therefore a postmarketing commitment to optimize the existing assay or develop an improved assay for detecting adventitious virus contamination in the unprocessed bulk harvest is recommended.

2) Because cytokines such as TNF α have been shown to downregulate the expression of cytochrome P450 enzymes (CYP) in humans, it is possible that inhibition of TNF with golimumab treatment may reverse the effect of the cytokine on CYP substrates, resulting in a normalization of CYP regulation and potential drug interaction with P450 substrate drugs upon initiation or discontinuation of golimumab treatment. Therefore a postmarketing commitment for in vitro or in vivo drug interaction studies to assess the potential effect of golimumab on Cytochrome P450 substrate drugs is recommended.

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References

Braun J and J Sieper, "What is the most important outcome parameter in ankylosing spondylitis?" *Rheumatology (Oxford)*, 2008, 47:1738-1740.

Clark, IA, "How TNF was recognized as a key mechanism of disease." *Cytokine Growth Factor Reviews* 18 (2007) 335-343.

Combe B, "Progression in early rheumatoid arthritis." *Best Practice & Research Clinical Rheumatology*, 2009, 23:59-69.

Cush JJ, "Biological drug use: US perspectives on indications and monitoring." *Annals of Rheumatic Disease*, 2005, 64:iv18-iv23.

Gladman DD, et al., "Psoriatic arthritis: epidemiology, clinical features, course, and outcome." *Annals of Rheumatic Disease*, 2005, 64:14-17.

Hundsberger H, et al., "TNF a moonlighting protein at the interface between cancer and infection." *Frontiers in Bioscience*, May 1, 2008, 5374-5386.

Schwabe RF and DA Brenner, "Mechanisms of liver injury: TNF- induced liver injury: role of IKK, JNK, and ROS pathways." *Am J Physiol Gastrointest Liver Physiol*, 2006, 290:583-589.

Sieper J, "Developments in the scientific and clinical understanding of the spondyloarthritides." *Arthritis Research & Therapy* 2009, 11:208

Zochling J and J Braun, "Assessment of ankylosing spondylitis." *Clin Exp Rheumatol* 2005, 23(suppl 39):S133-S141.