CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125289

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	April 24, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125289
Applicant Name	Centocor Ortho Biotech, Inc.
Date of Submission	June 24, 2008
PDUFA Goal Date	April 24, 2009
Proprietary Name / Established (USAN) Name	Simponi Golimumab
Dosage Forms / Strength	Pre-filled syringe or pre-filled syringe in autoinjector for subcutaneous injection, 50 mg
Proposed Indication	For the treatment of: ▪ Moderately to severely active rheumatoid arthritis, in adults in combination with methotrexate ▪ Active psoriatic arthritis in adults, alone or in combination with methotrexate ▪ Active ankylosing spondylitis in adults
Recommendation for action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Eric Brodsky, M.D.
Statistical Review	Jonathan Norton, Ph.D.; Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Gary P. Bond, Ph.D, DABT.; R. Adam M. Wasserman, Ph.D.; Paul C. Brown, Ph.D.
OBP Quality Review	Kurt Brorson, Ph.D.; David M. Frucht, M.D.; Kathleen A. Clouse, Ph.D.
Office of Compliance/DMPQ	Partricia F. Hughes, Ph.D.; Kalavati Suvarna, Ph.D.; Concepcion Cruz
Microbiology Review	N/A
Clinical Pharmacology Review	Lei Zhang, Ph.D.; Suresh Doddapaneni, Ph.D.; Venkatesh Atul Bhattaram, Ph.D.; Yaning Wang, Ph.D.
DDMAC	Mathilda Fienkeng; Sangeeta Waswani; Michael Sauers
DSI	Susan Liebenhaut, M.D.
CDTL Review	Sarah Okada, M.D.
OSE/DMEPA	Carlos M. Mena-Grillasca, R.Ph.; Kristina Arwine, Pharm.D.
OSE/DAEA	N/A
OSE/DRISK	Suzanne Berkman, Pharm.D.; Mary Dempsey; Sharon R. Mills, R.N.; Carlos M. Mena-Grillasca, R.Ph.; Kathy O'Connell, M.D.; Kendra Worthy, Pharm.D.; Claudia Karwoski, Pharm.D.
OSE/DEPI	N/A
CDRH/General Hospital Devices	Pandu R. Soprey, Ph.D.; Anthony Watson

OBP=Office of Biotechnology Products
DMPQ=Division of Manufacturing and Product Quality
OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
CDRH=Center for Devices and Radiological Health

1. Introduction

Golimumab is a human derived monoclonal antibody that targets Tumor Necrosis Factor-α (TNFα). The drug product, Simponi, neutralizes the activity of human TNFα by binding to the

soluble form and preventing the cytokine from binding to cell surface TNF receptors. TNF inhibition has been demonstrated to be beneficial in the treatment of rheumatoid arthritis (RA), psoriatric arthritis (PA) and ankylosing spondylitis (AS). Three of the currently four approved anti-TNFα products carry all three of these indications.

2. Background

Agreement with the sponsor regarding the development plan for Simponi resulted in a submission sufficient for filing and review. The sponsor has submitted the results from five Phase 3 clinical trials in support of the efficacy of Simponi for RA, PA and AS. These studies clearly establish the efficacy of the 50-mg dose for RA and of both the 50- and 100-mg doses for PA and AS. The safety profile of the product appears to be similar to the previously approved TNFα-inhibitor products. While an initial concern regarding adventitious viral contamination was raised during an establishment inspection, that finding has been thoroughly evaluated and is no longer of concern. The clinical pharmacology review team has recommended drug-drug interaction evaluations due to evidence suggesting that TNF-α down regulates cytochrome P450 expression (see discussion below).

3. CMC

On Page 6 of his review, Dr. Frucht states the following:

> The data submitted in this application support the conclusion that the manufacture of golimumab is well controlled, leading to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use (under conditions specified in the package insert).

During development and testing, there were a number of manufacturing changes, but the review team has determined that the product used in the preclinical and clinical studies is comparable to the to-be-marketed product. The sponsor's proposed 36-month expiry dating for the drug substance and 24-month expiry dating for the drug product were found to be supported by the stability data submitted in the application. Simponi will be distributed in 50 mg pre-filled syringes with a Centocor Autoinjector or [redacted] each intended for single use. The data submitted regarding these devices were reviewed by the CDRH team and found to be acceptable for approval. b(4)

During the review cycle, the sponsor notified FDA that adventitious virus had been detected in numerous cell culture harvest samples from golimumab and another monocolonal antibody product manufactured by Centocor. However, these assays were only positive at one testing facility, and were negative when replicated at two other contract testing laboratories. Inspection of the facility with the positive results determined that the root cause was a non-optimized assay, not initially evident due to insufficient attention to the negative control. The positive "foci" were determined to actually be cell clumping due to matrix effects, and was also found in the negative controls. Additional more advanced techniques also failed to detect

any virus, and the sponsor concluded that the original results were false positives. The Agency review team concurred with this conclusion and recommended a postmarketing commitment to optimize the existing assay or develop an improved assay for detecting adventitious viral contamination in the unprocessed bulk harvest.

4. Nonclinical Pharmacology/Toxicology

The non-clinical studies were performed in the cynomolgus monkey as golimumab demonstrated binding and neutralization of monkey TNFα, but not TNFα from mouse, rat or dog. No unexpected or unusual toxicities were noted in the non-clinical studies. While golimumab appeared to impair the T-cell Dependent Antibody Response when administered intravenously, impairment was not seen with subcutaneous administration, and clinical data did not demonstrate impaired responses to immunization at therapeutic doses. Although a five-fold increase in exposure was noted in pregnant compared to non-pregnant monkeys, the monkeys in the embryofetal study were older and heavier than the female monkeys in the other chronic toxicology studies, resulting in a two-fold higher total dose. The pregnant monkeys did not demonstrate any unusual toxicities.

5. Clinical Pharmacology/Biopharmaceutics

The following is reproduced from Dr. Okada's summary of the clinical pharmacology of Simponi on page 10 of her review:

> 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 1: 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%.

The exposure-response data generated by the sponsor did not demonstrate a consistent relationship in increasing doses from 50 mg every 4 weeks to 50 mg every 2 weeks to 100 mg every 4 weeks. The sponsor selected the 50 mg every 4 weeks and the 100 mg every 4 weeks doses for the Phase 3 trials. While the higher dose did not demonstrate added benefit and has not been submitted for approval in this application, [redacted] No clinically relevant differences between racial groups, different age groups, or between males and females were noted. No studies were performed in the pediatric population or in subjects with renal or hepatic impairment.

b(4)

A bioequivalence study of the two injection methods for Simponi delivery found equivalent AUC parameters by Agency standards. The CI for the Cmax, however, was 96% to 127%, slightly outside the upper limit of the standard 80% to 125% range. The clinical review team determined this small increase to be clinically irrelevant, particularly in light of the safety data available for the 100 mg dose studied in the clinical trials.

Although golimumab is not metabolized by cytochrome P450 enzymes (CYP), recent data have suggested that cytokines such as TNFα may down regulate the expression of CYP, potentially leading to decreased metabolism of CYP substrates. Conversely, cytokine antagonists are likely to reverse this down-regulation effect leading to increased metabolism of CYP substrates. Recent clinical data with tocilizumab (a IL-6 receptor antagonist) showed such an effect with a CYP3A substrate, simvastatin. Based on these findings with other products and the possibility that these drug interactions may have clinical implications for CYP substrates with narrow therapeutic indices, the clinical pharmacology review team has recommended a Phase 4 study to assess these possible interactions. DMARDs, NSAIDs and corticosteroids were evaluated for effects on golimumab pharmacokinetics via POP-PK analysis. The only effect noted was the apparent decreased clearance of golimumab in the presence of concomitant methotrexate (MTX) noted above.

On pages 13 and 14 of her review, Dr. Okada notes the following:

> 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.

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.

The sponsor responded to this post-marketing commitment request with a counterproposal for insertion of the following into the product labeling:

Cytochrome P450 Substrates
The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Upon review, Drs. Zhang, Doddapaneni and Okada determined that this language would be a suitable alternative to actually performing the proposed study as this is essentially what would have been required should the study have demonstrated a drug-drug interaction.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The applicant submitted the results of five clinical trials, three in RA and one each in PA and AS.

RA

- Study C0524T05 (T05) compared Simponi 100 mg monotherapy, Simponi 50 mg and 100 mg in combination with MTX, and MTX monotherapy administered sc monthly over 24 weeks. MTX was optimized to a dose of 20 mg once weekly by Week 20. The primary endpoint was the proportion of ACR50 responders at Week 24.

- Study C0524T06 (T06) compared Simponi 100 mg monotherapy, Simponi 50 mg and 100 mg in combination with stable doses of background MTX, and background MTX monotherapy administered sc monthly for 24 weeks in patients with inadequate response to MTX greater than or equal to 15 mg dosed weekly. The primary endpoint was the proportion of ACR20 responders at Week 14. If the study demonstrated a statistically significant treatment effect for the primary endpoint, a "co-primary" endpoint of improvement from baseline in HAQ-DI at Week 24 was to be tested.

- Study C0524T11 (T11) compared Simponi 50 mg, Simponi 100 mg or placebo administered sc monthly for 24 weeks as adjunctive therapy with background DMARDs in patients with inadequate response to DMARDs and a history of previous TNF inhibitor use. The primary endpoint was the proportion of ACR20 responders at Week 14.

For each of the studies, the sponsor employed a gate keeping sequence to address multiplicity across doses. If statistical significance was demonstrated for the results of the combined Simponi plus MTX or DMARD groups vs. the control group, than individual doses were to be tested against the control. The following table reproduced from page 16 of Dr. Okada's review summarizes the results of the three RA clinical trials:

Table 2: 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 monotx (n=159)	Golimumab + MTX 50 mg (n=159)	Golimumab + MTX 100 mg (n=159)	Golimumab + MTX 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 monotx (n=133)	Golimumab + MTX 50 mg (n=89)	Golimumab + MTX 100 mg (n=89)	Golimumab + MTX 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)	Golimumab +/- DMARDs 100 mg (n=153)	Golimumab +/- DMARDs 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

Studies T06 and T11 provided clear evidence of efficacy for Simponi on the primary endpoints and the secondary endpoints were supportive as well. In regard to the absence of a statistically significant treatment effect in Study T05, Dr. Okada notes the following on page 16 of her review:

> 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. 053), 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 [...] 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.

The sponsor is not seeking approval of Simponi for monotherapy treatment of RA [redacted] The results of the three trials, as noted previously, do not demonstrate additional benefit of a 100-mg dose of Simponi compared to a 50-mg dose, and the sponsor is not seeking approval of the higher dose. The clinical review team is also recommending inclusion of the physical function data in the product label, to allow a claim for this outcome. The HAQ-DI results demonstrated a statistically significant treatment effect in Study T06 as a co-primary endpoint, and this result was replicated in Study T11 in which the HAQ-DI was analyzed as a secondary outcome measure. The results of the HAQ-DI evaluations in the three RA trials are summarized in the following table reproduced from page 18 of Dr. Okada's review:

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Table 3: HAQ-DI Results in the Golimumab RA Trials

HAQ-DI Results in the Golimumab RA Trials					
Study T05 (MTX naïve)	MTX + pbo (n=160)	Golimumab 100 monotx (n=159)	Golimumab + MTX 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 + pbo (n=133)	Golimumab 100 monotx (n=133)	Golimumab + MTX 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 + pbo (n=155)		Golimumab +/- DMARDs 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

PA

Study C0524T08 (T08) compared Simponi 50 mg, Simponi 100 mg and placebo administered sc monthly in PA patients with or without concomitant background MTX for 24 weeks. From Week 24 to Week 52 the blind was maintained, but the placebo subjects were crossed over to active treatment with Simponi 50 mg. At Week 52 all subjects entered an open-label extension period to Week 268. The primary endpoint was the proportion of ACR20 responders in the combined Simponi group at Week 14 compared to placebo. Dr. Okada's Table 6 summarizes the results of the primary endpoint analysis and is reproduced from page 19 of her review below:

Table 4: 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

The results of the secondary endpoint analyses were supportive of the primary endpoint analysis. Again, the review team found the physical function evaluation to demonstrate a statistically significant treatment effect for the HAQ-DI and recommends inclusion of these results in the product label.

AS

Study C0524T09 (T09) compared Simponi 50 mg, Simponi 100 mg and placebo administered sc monthly in AS patients with or without concomitant background DMARDs for 24 weeks. From Week 24 to Week 104 the blind was maintained, but the placebo subjects were crossed over to active treatment with Simponi 50 mg. At Week 104 all subjects entered an open-label extension period to Week 268. The primary endpoint was the proportion of subjects in the combined Simponi arms achieving an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14 compared to the subjects in the placebo arm. Dr. Okada's Table 8 summarizes the results of the primary endpoint analysis and is reproduced from page 21 of her review below:

Table 5: 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

The results of the secondary endpoint analyses were supportive of the primary endpoint analysis.

8. Safety

A total of 2894 subjects received at least one dose of Simponi in the clinical development program. In the five Phase 3 trials 2057 subjects were exposed to Simponi for at least 24 weeks, with 1768 subjects exposed for at least 52 weeks. There were 13 deaths in the controlled and uncontrolled portions of the rheumatology studies: one on placebo, four on

Simponi 50 mg, and eight on Simponi 100 mg. In the controlled portions of the Phase 3 trials, one patient died in the placebo arms, one in the Simponi 50-mg arms, and two in the Simponi 100-mg arms. Drs. Brodsky and Okada assessed these deaths as "typical" of RA, PA and AS patients. The only death they felt raised concern due to a possible relation to Simponi exposure occurred in a young Korean woman with early RA treated with Simponi 100 mg who had underlying liver disease, exposure to multiple hepatoxic medications, and then developed hepatosplenomegaly and symptoms of hepatitis. The subject died following a liver biopsy that resulted in massive post-procedural hemorrhage. They also note that, based on the incidence of deaths per 100-patient years exposure in the controlled portions of the Phase 3 trials, the rates of death were lower than published background rates in the RA population. While I agree that the rates were lower (by nearly an order of magnitude), there did appear to be a dose effect for the deaths in the Simponi 50- and 100-mg arms in both the controlled portions and the combined controlled and uncontrolled portions of the Phase 2 and 3 studies. Nevertheless, upon my review, the individual events are for the most part not likely to be related to exposure to Simponi and there is no consistent trend in the types of adverse events leading to death.

Serious adverse events and adverse events leading to discontinuation occurred in relatively low numbers and there did not appear to be a higher incidence in the Simponi-treated subjects compared to the placebo-treated subjects, with the exception that events of an infectious nature did appear to occur at a higher rate in the Simponi-treated subjects, particularly those treated with the 100-mg dose. Dr. Okada discusses the infectious adverse events in the following, reproduced from page 22 of her review:

> 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.

While the overall exposure-adjusted incidence of malignancy in the Simponi-exposed subjects was similar to controls, there was an increased incidence of lymphoma in Simponi-treated subjects and Simponi treatment in a Phase 2 asthma study was associated with an increased incidence of malignancy. Five of the eight subjects diagnosed with a malignancy were in the 200-mg Simponi treatment group, two were in the 100-mg treatment group, and one was in the 50-mg treatment group; none of these cancers occurred in the placebo group. However, the number of cases was low and these findings are not dissimilar to what was seen with the approved TNF blocking agents.

Adverse events occurred in 75% of subjects in each of the Simponi groups and 70% of subjects in the control groups. The most frequent adverse events in the Simponi-treated subjects were: upper respiratory tract infections, nasopharyngitis, nausea, headache and fatigue.

Transaminase elevations were common in the Simponi-exposed subjects, but were also high in the control-treated subjects. This is consistent with what has been seen with other TNFα inhibitors and with the fact that the subjects in the Simponi studies were often on concomitant treatment with a variety of hepatotoxic medications or had other etiologies for liver disease. Four Simponi-treated subjects in the overall database (0.14%) and 2 control-treated subjects (0.26%) developed liver enzyme abnormalities consistent with Hy's Law criteria for severe drug-induced liver injury. Of these patients, one patient in the golimumab 100-mg group died of massive post-procedural hemorrhage following a liver biopsy and one patient in the placebo group experienced clinical hepatitis symptoms including nausea, fever, and jaundice. The rest of these patients were asymptomatic and liver enzymes resolved. While 2% of the Simponi-treated subjects and only 0.5% of the control-treated subjects developed neutropenia or leucopenia, the events were transient and not associated with clinical adverse events.

Two percent of the subjects in both dose groups of Simponi who were on background MTX treatment developed anti-golimumab human-anti-human-antibodies compared to 7% of the subjects not treated with MTX. However, based on the clinical review team's evaluation, these subjects did not experience lack of response or loss of efficacy; nor did they develop an increased risk of allergic reactions. There were also slightly higher incidences of urticaria, rash and injection site reactions that appeared to be dose-related. In the Simponi-treated subjects, one patient developed new onset cutaneous lupus, two developed vasculitis, and six developed new-onset pustular psoriasis. No control-treated patient developed an autoimmune disorder. However, the exposure-adjusted incidence of autoimmune disorders was similar in the Simponi and control groups. No clinically relevant reduction in response to immunization was noted in the Simponi-treated subjects.

Four subjects developed CHF. Three of these were on Simponi and one was on placebo. TNF inhibitors have been shown to worsen CHF in exploratory clinical trials and, therefore, it is plausible that being on Simponi might result in unmasking of latent CHF. However, there is no evidence to suggest that these drugs actually cause CHF. There was a single case of possible multiple sclerosis, but the patient had possible prodromal symptoms even before treatment. It is unclear if Simponi resulted in worsening of this event.

9. Advisory Committee Meeting

This is the fifth anti-TNFα antibody product submitted for licensure, and a great deal is already known about this class of biologic products after over a decade of use in patients with arthritis. This in addition to the fact that the review team found no surprising product safety signals or efficacy concerns, and that the efficacy of the product was clearly established in the clinical trials, led to a decision that discussion at advisory committee was not necessary.

10. Pediatrics

We are waiving the pediatric study requirement for psoriatic arthritis and ankylosing spondylitis indications for children 0 to 16 years of age, and for the juvenile idiopathic arthritis

indication for children 0 to less than 2 years of age because these studies would not be feasible due to extremely small pediatric patient populations in these diseases.

We will defer submission of a juvenile idiopathic arthritis pediatric study of children 2 to 16 years of age because this product is ready for approval for use in adults and the pediatric study has not been completed. The sponsor will be required to assess the pharmacokinetics, safety, immunogenicity, and efficacy of golimumab in pediatric patients 2 to 16 years of age with active polyarticular juvenile idiopathic arthritis.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

The Agency and the sponsor have concurred on appropriate language for the product labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action

  Approval

- Risk Benefit Assessment

The sponsor has provided clear evidence of the efficacy of Simponi in the treatment of RA, PA and AS. While the product has serious risks associated with its use, such as the increased risks of life-threatening infections and malignancies, these events are uncommon and do not appear to occur more frequently than those seen with the other approved products in this class. RA, PA and AS are severely debilitating diseases which often respond only partially to non-biologic disease modifying agents. Simponi, as with the other approved TNF blockers, provides a level of effective amelioration of the signs and symptoms of RA, PA and AS that clearly outweighs the risks associated with its use.

- Recommendation for Postmarketing Risk Management Activities

  No PMRs are required for this application other than the pediatric study requirement noted above.

- Recommendation for other Postmarketing Study Commitments

  The OBP quality review team has recommended that the sponsor optimize the existing adventitious virus assay or develop an improved assay for use at all

contract locations performing adventitious virus contamination testing of unprocessed bulk harvest. I concur with this recommendation.