CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125289

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	April 24, 2009
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II 4/24/09
Subject	Summary Review
NDA/BLA # Supp #	125289
Applicant Name	Centocor, Inc.
Proprietary / Established (USAN) Names	Simponi Golimumab
Dosage Forms / Strength	Pre-filled syringe or pre-filled syringe in autoinjector for subcutaneous injection, 50 mg
Proposed Indication(s)	For the treatment of: 1. Moderately to severely active rheumatoid arthritis, in adults in combination with methotrexate 2. Active psoriatic arthritis in adults, alone or in combination with methotrexate 3. Active ankylosing spondylitis in adults
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding golimumab and the reader should refer to the reviews in the action package for a more detailed discussion. As is summarized in Dr. Okada's review, golimumab is a humanized monoclonal antibody that binds and neutralizes the activity of Tumor Necrosis Factor-α(TNF) preventing the initiation of downstream signaling cascades. At present, there are four TNF inhibitors approved in the United States (dating back to 1998 for the initial approval of infliximab) including infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira) and certolizumab (Cimzia). Therefore, we have a great deal of experience with this class of drugs.

As stated in Dr. Okada's review, this develop program included five pivotal trials, including three trials in rheumatoid arthritis (RA) subjects and one trial each in psoriatic arthritis (PsA) and ankylosing spondylitis (AS). This approach, using the data demonstrating efficacy in at least two adequate trials from one disease (typically RA) as support which then requires only one pivotal study for closely related indications has been historically accepted by the rheumatology group.

In regard to discussions of CMC, pharmacology/toxicology and clinical pharmacology/biopharmaceutics, I refer the reader to Dr. Okada's excellent review and Dr. Rappaport's review with which I am in agreement.

Efficacy

This has been thoroughly covered in Dr. Okada's review and I will only highlight the results here. The results of the trials in regards to RA, PsA and AS are presented in the three tables below from Dr. Okada's review.

In regard to the RA trials, all were based on the ACR response criteria, which is a composite endpoint of 7 core variables (swollen joint count, tender joint count, physician's assessment of disease activity, patient's assessment of: (1) disease activity (2) pain and (3) physical function, and levels of acute phase reactants. The response rate (20%, 50% or 70%) is in regard to that percentage of improvement in both tender joint count and swollen joint count and at least that percentage of improvement in three of the other five variables.

Table 1: Primary Endpoint Results in the Golimumab RA Trials

Primary Endpoint Results in the Golimumab RA Trials					
Study T05 (MTX naive)	MTX + pbo (n=160)	Golimumab 100 monotx (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 monotx (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

As noted in Dr. Okada's review, while golimumab was not shown to be superior to MTX (by strict alpha criteria) in MTX naïve subjects (Study T05), this is not unexpected as TNF inhibitors rarely demonstrate superiority to optimized MTX in this population. All other trials demonstrate the efficacy of golimumab on primary and most secondary endpoints in RA. Also noted by Dr. Okada is that, while the 100 mg dosage did not demonstrate efficacy beyond the 50 mg dose utilizing the above evaluation criteria, [redacted] b(4)

As per previous guidance from the rheumatology group, in closely related diseases, the data from one disease (typically RA) that has demonstrated efficacy in at least two adequate trials can be used to support a single adequate trial conducted in the other indications. The results for PsA (which also uses ACR as a primary) are demonstrated in the table below from Dr. Okada's review.

Table 2: 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 primary endpoint for AS is the ASessment in Ankylosing Spondylitis (ASAS) 20 response, which is defined as relative improvement of >/= 20% from baseline and absolute improvement of >/= 1 cm on 0 to 10 cm scales in at least three of four domains: patient (1) global assessment (2) pain, inflammation-related back stiffness and physical function. Results are in the table below from Dr. Okada's review.

Table 3: 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

Based on the above results, golimumab appears to have efficacy in RA, PsA and AS.

Safety

The safety findings for this application are consistent with previous clinical experience with other TNF inhibitors. While this group of drugs can have serious and life-threatening safety issues that should not be minimized, golimumab did not appear to have an additional risk to those already identified for other agents. The risks in regard to infection and all the other typical adverse events are reviewed in Drs. Okada and Brodsky's reviews and do not seem excessive compared to the already available agents. Other agents in this group have REMS and extensive labeling identifying the risks, all of which that should apply to golimumab.

I would like to mention the issue of TNF and malignancy. In a recently published article (Am J Respir Crit Care Med Vol 179. pp549-558, 2009), where golimumab was used in the treatment of severe persistent asthma, there was noted to be an imbalance in the occurrence of malignancy in subjects receiving active agent compared to those not. Our internal review of this data is also consistent with this conclusion. A summary of malignancies is presented in the table below.

Malignancy reports from Asthma trial through week 76

		Golimumab		
N	78	75	78	78
	Placebo	50 mg	100 mg	200 mg
Subjects with malignancies	0	1 (1.3)	2 (2.6)	5 (6.4)
B-cell lymphoma			1	
Basal Cell				2
Breast		1		
Cervical				1
Colon				1
Melanoma			1	
Renal				1

Study day at the time of diagnosis ranged from Day 76 to Day 448. From this table, it would appear that there may be a dose related effect in regard to malignancy in an asthmatic population. As with most of the safety issues that we face where we have a small number of events, it is difficult to know whether this represents a true signal or not, and if there is a true signal, whether there might be differences in the subject population such that the drug may have one effect in one population but not another.

On the one hand, as Dr. Okada points out, there are theoretical reasons why this may be a true finding in that TNF itself may induce apoptosis, thus have an effect against potentially malignant cells, or at least TNF inhibition may set up a permissive environment to allow already malignant cells to grow. There have been noted imbalances in other agents used to treat arthritides and this finding is in the other agents' labels. On the other hand, if one were to eliminate some of the cases above where there was limited exposure, or remove the non-melanoma skin cancers as we sometimes do in the evaluation, or remove lymphoma, then the appearance of a dose response disappears. Such is the dilemma when we are dealing with small numbers of events.

I do draw some comfort in the tables regarding malignancy from Dr. Brodsky's review presented below. These tables would seem to indicate that, at least when compared to other agents used in RA in subjects with rheumatologic diseases, golimumab does not have an increased risk.

Table 7.4.6: All malignancies in the controlled and uncontrolled portions of the Phase 2 and Phase 3 rheumatology trials of SC golimumab through the last safety cut-off[1]

	Controlled Portions of Phase 3 Trials (through Week 24)			Controlled & Uncontrolled Portions of Phase 2 and Phase 3 Trials (through last Safety Cut-Off)[1]	
	placebo ± MTX	golimumab50 ± MTX	golimumab100 ± MTX	golimumab50 ± MTX	golimumab100 ± MTX
Patients treated	639	683	977	1301	1356

Patient-years of follow-up[3]		252	294	443	1467	1757
Median patient-years of follow-up		—	—	—	1.2	1.5
All Malignancies except NMSC	n of patients	2	1	5	11	8
	Incidence per 100 patient-years	0.8	[redacted]	[redacted]	[redacted]	[redacted]
NMSC	n of patients	3	1	6	9	11
	Incidence per 100 patient-years	1.2	[redacted]	[redacted]	[redacted]	[redacted]

1 As of the last safety cut-off date in the 120-Safety Update (i.e., June 2, 2008). Patients may appear in more than one column.

2 The rheumatologic Phase 2 and Phase 3 Trials included 1 Phase 2 RA (Study 2), 3 Phase 3 RA (Studies 5, 6, and 11), 1 Phase 3 PsA (Study 8), 1 Phase 3 AS (Study 9).

Adapted from the 120-Safety Update Report, Appendix A.32, Pages 381-3

Table 7.4.7: Malignancies in the controlled and uncontrolled portions of the SC golimumab rheumatology Phase 2 and Phase 3 trials through the last safety cut-off compared to the SEER database[1]

			placebo ± MTX	golimumab ± MTX
All Malignancies	All malignancies except NMSC[3]	Median patient-years of follow-up	0.5	1.4
		Total patient-years of follow-up	344	3099
		Observed # of patients with ≥ 1	2	19
		Observed incidence per 100 patient-years	0.6	0.6
		Expected # of patients with ≥ 1 (SEER)[2]	2.1	17.6
		SIR (95% CI)[2]	1.0 (0.1, 3.5)	1.1 (0.7, 1.7)
	NMSC[4]	Total patient-years of follow-up	342	3087
		Observed # of patients with ≥ 1	5	19
		Observed incidence per 100 patient-years	1.5 (0.5, 3.4)	0.6 (0.4, 1.0)

b(4)

1 Based on the SEER database from 2004, adjusted for age, gender, and race. Patients may appear in more than one column. This table includes the results from all the rheumatologic trials of SC golimumab (5 Phase 3 trials and the 1 Phase 2 RA trial). The Phase 1 studies in patients with RA, the studies in healthy volunteers, and patients with ▬ are not included in this table. The Phase 2 asthma study is not included. The malignancies in the IV golimumab program in RA in Study 12 are not included in this table.

2 SIR is the standardized incidence ratio (**observed** number of patients with malignancy **divided by** the **expected** number of patients with malignancy).

3 All malignancies except NMSC includes lymphomas. There were 3 lymphomas in the golimumab groups and no lymphomas in the placebo groups (see Table 7.4.8).

4 Since the SEER database does not include NMSCs, no comparison was made to the SEER database.

Adapted from the 120-Safety Update Report, Appendix A.33, Pages 384-385; Appendix A.34, Page 386-388Appendix A.36, Pages 392-394

While the data above also has a limited number of events, it includes much greater numbers exposed subjects (2057 for at least 24 weeks and 1768 for at least 52 weeks) and would seem to indicate that, at least in the population of subjects studied for this application, there does not appear to be an increase in malignancy (excluding lymphoma). In any event, labeling should be cautionary and indicate the uncertainty we have with this issue.

Advisory Committee Meeting

Golimumab is the fifth TNF inhibitor to come to market and does not appear to be associated with a unique safety or efficacy issue compared to the other agents. Therefore, an advisory committee meeting was not convened.

Conclusions and Recommendations

I agree that golimumab has demonstrated efficacy and has an expected safety profile for a TNF inhibitor when used in subjects treated for RA, PsA and AS and, if appropriate labeling can be agreed upon with the sponsor, it should be approved for these indications.