

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125276/S049

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 22, 2012
From	Sarah (Okada) Yim, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	sBLA 125276/49
Supplement#	
Applicant	Hoffman La Roche, Inc.
Date of Submission	December 13, 2011
PDUFA Goal Date	October 12, 2012
Proprietary Name / Established (USAN) names	Actemra (tocilizumab)
Dosage forms / Strength	Single use vials of 20 mg/mL: 80 mg/4mL, 200 mg/10mL, 400 mg/20 mL, for IV infusion
Proposed Indication(s)	1. Rheumatoid Arthritis <ul style="list-style-type: none"> a. Change in population from TNF-inhibitor inadequate responders to (b)(4) with moderately to severely active RA
Recommended:	<i>Approval, with revisions to proposed label</i>

1. Introduction

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin-6 receptor (IL-6R). Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6. IL-6 is a pleiotropic cytokine that has important roles in the regulation of the immune response, inflammation, and hematopoiesis. IL-6 is the primary driver of acute phase reactants, and hepatocytes express high levels of IL-6R. Elevated tissue and serum levels of IL-6 have been implicated in the pathophysiology of RA.

The original biologic license application (BLA) for tocilizumab in rheumatoid arthritis (RA) was submitted November 19, 2007, and received a complete response on September 17, 2008, due to deficiencies in the nonclinical program and on inspection of the manufacturing facilities. These deficiencies were addressed in a complete response submission which was submitted July 9, 2009 and approved on January 8, 2010. Subsequent supplemental BLAs have been approved to include additional efficacy data in RA for inhibition of structural damage, improving physical function, and major clinical response (Supplements 7, 10, and 11, approved in January 2011) and also to include a new indication of systemic juvenile idiopathic arthritis (SJIA), approved in April 2011.

The present supplement was submitted with the intent of revising the label to expand the indicated population of RA patients from those who have had an inadequate response to TNF

inhibitors to (b) (4) with moderately to severely active RA. The 5 pivotal studies submitted in the original BLA included the range of RA patients, with 1 trial in patients who had failed at least one TNF inhibitor, 3 trials that were in patients who had failed at least one DMARD, and 1 trial in methotrexate naïve/early RA patients. The efficacy of tocilizumab was demonstrated in all 5 trials. Because it was first-in-class and had some different potential toxicities compared to other approved biologic immunosuppressives, TCZ was approved in the TNF-inadequate responder population initially, pending longer-term exposure to confirm that the observed safety profile would remain consistent and adverse outcomes of longer latency (such as cardiovascular adverse events related to lipid changes) would not become an issue. The data in this submission represents 65099 patient-years of exposure, based on post-marketing data, as well as an updated assessment of safety data from the applicant's ongoing open-label long-term extension studies (WA17823, WA18695, and WA18696).

2. Background

The clinical data submitted in the original BLA for TCZ were derived from 5 randomized, double-blind, controlled trials of TCZ in 4211 RA patients with moderately to severely active disease. These data provided substantial evidence of the efficacy of TCZ for the treatment of RA via a statistically significant improvement in the proportion of ACR20 responders in the TCZ-treatment groups of each of the studies at Week 24, the primary endpoint assessment for these studies. The global safety database at that time included approximately 4700 patients and over 7900 patient-years of exposure. Major safety signals observed included an increased risk of serious infections and GI perforations, and abnormalities of laboratory parameters, including decreased white blood cell count, increases in lipids, and liver enzyme elevations, although these were not associated with serious clinical adverse events in the controlled setting of the clinical trial experience. Malignancies and demyelinating adverse events were observed in the clinical trials; however the relative risk and role of TCZ treatment in the development of these adverse events was not well-defined.

Due to concern that TCZ-related lipid elevation could increase the risk of cardiovascular adverse events, at the time of approval a post-marketing requirement (PMR) for a randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events was enacted. This trial is not scheduled to complete until 2018. However, as data have continued to accrue and have been submitted, the incidence of serious cardiovascular events has remained consistent with the original BLA, in that the incidence does not appear to be elevated. Thus the Applicant inquired at a pre-sBLA teleconference in November 2011 whether it would be acceptable to submit a sBLA to expand the indicated population prior to the completion of the aforementioned PMR study, and the Agency agreed to evaluate a submission in this regard. Other agreements were reached on the assumptions used to estimate the TCZ PY of exposure in the postmarketing setting based on sales data for the TCZ global postmarketing safety database, the use of the long-term extension studies for WA17823, WA17824, WA18696 as the sensitivity analyses, the use of the Thomson Reuters MarketScan Healthcare databases for generating event rates in RA patients treated with TNF antagonists, the safety data and analyses to assess potential risks associated with TCZ treatment regarding

increases in serum hepatic aminotransferase levels, increases in LDL cholesterol, and GI perforations, and the data package to evaluate other AEs of interest.

3. CMC/Device

No CMC information or changes were submitted with this efficacy supplement. Actemra is approved as liquid-in-vial for intravenous infusion.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted with this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology/biopharmaceutics data were submitted with this efficacy supplement.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new efficacy data were submitted in this supplement. The original BLA was approved on the basis of efficacy in reducing the signs and symptoms of RA, which was captured by the proportion of patients achieving an American College of Rheumatology (ACR) “20” response (i.e., 20% improvement). ACR responses are summarized in Table 1 below. In each of the RA patient populations assessed in the pivotal trials, TCZ treatment was associated with a greater proportion of patients achieving ACR 20, 50, and 70% levels of improvement. These differences were statistically significant.

Study WA17823 was a 1-year controlled study in patients who had failed at least one DMARD (also known as DMARD-inadequate responders, or DMARD-IR) that also served as the basis for the approval of the inhibition of structural damage, improvement in physical function, and major clinical response efficacy claims in a subsequent supplemental BLA.

Therefore the overall evidence of efficacy of TCZ in RA is derived from and applicable for the extended RA population being sought in this supplemental application.

Table 1: Summary of ACR Responses in the 5 Pivotal RA Studies

Percentage of ACR Responders at Week 24 in the 5 Pivotal RA Studies, by Trial Treatment (ITT Populations)					
Study	Pbo + DMARD**	TCZ 4mg/kg + DMARD**	TCZ 8mg/kg + DMARD**	p-value (4 mg/kg)	p-value (8 mg/kg)
Patients with incomplete response to MTX or other DMARDs					
WA17822	(n=204)	(n=213)	(n=205)		
ACR20	26	48	58	<0.0001	<0.0001
ACR50	11	32	44	<0.0001	<0.0001
ACR70	2	12	22	<0.0001	<0.0001
WA17823	(n=393)	(n=399)	(n=398)		
ACR20	27	51	56	<0.0001	<0.0001
ACR50	10	25	32	<0.0001	<0.0001
ACR70	2	11	13	<0.0001	<0.0001
WA18063	(n=413)		(n=803)		
ACR20	24		61		<0.0001
ACR50	9		38		<0.0001
ACR70	3		20		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment					
WA18062	(n=158)	(n=161)	(n=170)		
ACR20	10	30	50	<0.0001	<0.0001
ACR50	4	17	29	<0.0001	<0.0001
ACR70	1	5	12	0.1005	0.0002
MTX naïve/Early RA patients					
Study	MTX	TCZ 8 mg/kg	Tx Diff	95% CI	p-value
WA17824	(n=284)	(n=286)			
ACR20	52	70	0.19	(0.11,0.27)*	<0.0001
ACR50	34	44	0.12	(0.04,0.20)	0.0023
ACR70	15	28	0.14	(0.88,27.59)	0.0002

8. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing**

The clinical safety information submitted with supplement was derived from the following sources:

- **Placebo-Controlled Studies**

Safety data from the placebo-controlled periods of the five Phase 3 studies, organized by patient population, have been included in the overall safety analyses. The DMARD-IR patients were pooled from studies WA17822, WA17823, and WA18063, the TNF inhibitor inadequate responder (TNF-IR) patients were enrolled in study WA18062, and study WA17824 enrolled patients who were MTX-naïve. The placebo-controlled periods were all 24 weeks in duration except for study WA17823, which was blinded for 52 weeks. It should be noted that the term placebo used in this review refers to the corresponding placebo control which included patients exposed to placebo, MTX, and/or other DMARDs. Of the 4,098 patients randomized to treatment in the original TCZ Phase 3 studies, 3,028 (74%) were DMARD-IR. The remainder

of patients included 498 (12%) who were TNF-IR, 383 (9%) MTX-naïve patients, and 189 (5%) MTX-nonresponders; 2,644 (65%) patients received TCZ and 1454 (35%) patients received placebo. The total patient-year (PY) duration across all placebo-controlled populations was 1,560 PY for TCZ-treated patients and 743 PY for the corresponding placebo-treated patients.

- **Long-Term Extension (LTE) Studies**

Cumulative TCZ safety data are included up to April 1, 2011 and provides an additional 14 months of long-term safety data compared to the safety data submitted in the applicant's previous sBLA. This corresponds to an additional 2700 PYs duration of exposure for analysis. Data from the LTE safety dataset includes all patients who received at least one dose of double-blind and/or open-label TCZ in the Phase 3 studies. A total of 4009 patients who received at least one dose of TCZ are included in the LTE all-exposure population. There was a total of 14,994 PY of duration compared to 12,293 PY in the last submission. The median duration on trial for the overall LTE population was 4.6 years. A total of 1,241 patients enrolled in the LTE studies were from the US and 2,768 were from other countries. Consistent with the RA population, the majority of the PY duration data comes from female patients between 40 and 65 years of age. Of the 4009 patients, 700 (17%) were exposed for ≤ 12 months, 884 (22%) for 13 to 38 months, and 2425 (61%) were exposed for ≥ 4 years.

- **Postmarketing Global Safety Database**

Data used in the current safety analyses are based on the sponsor's postmarketing safety database of TCZ-treated patients recorded through July 29, 2011. This database includes all spontaneous reports from RA patients, the Japanese postmarketing surveillance program (JPMS), published reports, and from the sponsor's ongoing unblinded and open-label postmarketing studies. Based on the global sales data and the sponsor-supplied postmarketing trials, the estimated total PYs of exposure to TCZ calculate for the postmarketing event rate analyses was 65,099 PY. The majority of data is based on sales data from the ROW and Japan regions. The applicant estimates that the number of patients comprising this exposure includes roughly 68,447 patients. Of these, approximately 40,384 patients were exposed for 12 months or less, 19,165 exposed for 12 to 24 months, and 8,898 were exposed for 24 months or longer. The applicant used the MarketScan Healthcare Claims Database as well as the medical literature and other epidemiological data sources such as the US National Vital Statistics Reports and the US Surveillance and Epidemiology End Results (SEER) database to estimate background incidence rates for comparative analyses.

Safety Overview

Overall, the data in this submission remain consistent with safety data previously submitted for tocilizumab. The major risk of TCZ is serious infections, consistent with its potent immunosuppressive effects. TCZ manifested effects on laboratory parameters, such as decreased white blood cell count, increases in lipids, and most significantly, liver enzyme elevation, although these do not appear to be associated with an increased risk of associated clinical adverse events. Malignancies have not increased over time, and are consistent with background rates of malignancy in RA patients. GI perforation events continue to slowly accrue, but the exposure-adjusted incidence of GI perforations is not increasing. Compared to

other biologic immunosuppressive agents such as TNF inhibitors, the risk may be slightly higher, but remains below the expected incidence associated with corticosteroid treatment. Demyelinating adverse events remain a rare occurrence, and TCZ-treatment does not appear to be associated with an increased risk. The only notable change in the safety profile of TCZ is the occurrence of two cases of fatal anaphylaxis in the post-marketing experience, including one case in which the patient received pre-medication for the infusion. These cases prompted the applicant to propose additional labeling changes to highlight this risk.

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

Deaths

Overall, the rates and etiologies of mortality observed in this submission are consistent with the original BLA submission, other subsequent submissions for tocilizumab and the historical experience with other potent biologic immunosuppressives. Infections are the most common etiology, followed by cardiovascular disease, malignancy, and a smattering of less common etiologies. The etiologies observed are consistent with the underlying patient population. RA patients are known to have an increased background risk of mortality, approximately 1.5-1.7-fold the general population, and the most common causes of mortality in RA patients are cardiovascular disease and infection.¹ A total of 15/4098 (0.4%) patients (10/2644 on TCZ and 5/1454 on placebo) died during the placebo-controlled clinical studies, all of which were reported in previous submissions. An additional 75/4009 (2%) patients have died during the cumulative exposure period in the long-term extensions of the studies through the April 2011 cut-off date for this summary of clinical safety. In the postmarketing data, a total of 253 in an estimated 68,447 (0.4%) patients were reported to have died while on TCZ-treatment. Exposure-adjusted rates of death are summarized in Table 2, below.

Table 2: Rate of Death per 100 Patient-Years, by Analysis Population

	TCZ				Epidemiology Data for TNF Antagonists
	Placebo-controlled Data in DMARD-IR Patients		LTE Studies	Postmarketing Data	
	Placebo	All TCZ			
PY exposure	543	1496	14994	65099	3800
Rate of Deaths	0.74	0.47	0.57	0.39	0.61
95% CI	(0.20, 1.89)	(0.19, 0.96)	(0.45, 0.70)	(0.34, 0.44)	(0.38, 0.91) ^a
SMR ^b			0.86		
95% CI	NA	NA	(0.69, 1.06)	NA	NA

NA: not applicable; SMR: standard mortality ratio

a Unadjusted mortality rate for RA patients treated with TNF antagonists; calculated by the sponsor based on a meta-analysis data of 17 trials with 23 combined deaths over 3800 combined subject years exposure in 4097 patients [10177].

b Based on US mortality rates from the US National Vital Statistics Reports for 2009.

Source: Table 24 of Summary of Clinical Safety

¹ Sokka et al., Clin Exp Rheumatol 2008; 26(Suppl. 51):S35-S61.

Serious Adverse Events

The overall rate of Serious Adverse Events (SAE) in TCZ-treated patients appears generally consistent in the analysis populations and comparable to rates observed in trials of TNF inhibitors (see Table 3 below). Infections remain the most common cause of serious adverse events in all analysis populations. Gastrointestinal, Injury/Poisoning/Procedural Complications, Nervous, Cardiac, and Neoplasm/Malignancy system-organ-classes (SOC) were among the most common SAE in all analysis populations. Serious infections, malignancies, GI perforations, cardiovascular disorders, demyelinating disorders and anaphylaxis will be addressed individually in the sections that follow.

Table 3: Rate of Serious Adverse Events per 100 Patient Years, by Analysis Population

	Data in TCZ-Treated Patients				
	Controlled DMARD-IR Data		LTE Studies	Post-marketing	Epidemiol. Data
	Placebo	All TCZ			
PY exposure	543	1268	14994	65099	3032
<u>All serious adverse events</u>					
Rate	11.24	13.88	14.63	8.30	16.46 ^a
(95% CI)	(8.60, 14.44)	(11.90, 16.09)	(14.03, 15.26)	(8.08, 8.52)	(15.05, 17.97)
No of events	61	176	2194	5403	not reported
<u>Infections and infestations</u>					
Rate	3.13	4.57	4.46	2.31	
No of events	17	58	668	1507	
<u>Injury, poisoning, and procedural complications</u>					
Rate	0.74	1.50	1.27	0.39	
No of events	4	19	191	251	
<u>Gastrointestinal disorders</u>					
Rate	0.74	1.34	1.23	0.76	
No of events	4	17	184	493	
<u>Nervous system disorders</u>					
Rate	0.74	1.10	0.83	0.49	
No of events	4	14	125	319	
<u>Neoplasms, benign, malignant, and unspecified</u>					
Rate	0.55	0.95	1.18	0.35	
No of events	3	12	177	228	
<u>Cardiac disorders</u>					
Rate	0.55	0.63	1.05	0.41	
No of events	3	8	158	266	

a=Based on unadjusted incidence rate for TNF-antagonist treated RA patients from 18 randomized trials with 499 combined SAEs over a cumulative 3032 PY of follow-up in 3581 patients

Source: Tables 32, 34, 35, and 36 of Summary of Clinical Safety

Serious Infections

The rate of serious infections was highest in the early period (controlled period) of treatment with TCZ and did not increase over time in the LTE and post-marketing experience. Serious

infection events (SIE) of pneumonia were among the most common individual types of infections and occurred at a similar rate to that reported in the population, in whom immunosuppressive treatment would be typical. Serious opportunistic infections, tuberculosis and fatal infections appeared to occur at rates consistent with those observed with other potent immunosuppressives.

Table 4: Rate of Serious Infections per 100 Patient Years, by Analysis Population

	Data in TCZ-Treated Patients				
	Controlled DMARD-IR Data		LTE Studies	Post-marketing	Epidemiol. Data
	Placebo	All TCZ			
PY exposure	543	1268	14994	65099	
<u>Serious infections</u>					
Rate	3.13	4.57	4.46	2.31	4.2 ^a
No of events	17	58	668	1507	not available
<u>Serious opportunistic infections</u>					
Rate	-	0.16	0.07	0.09	0.07 ^b
No of events	0	2	10	58	not available
<u>Tuberculosis</u>					
Rate	-	-	0.11	0.04	0.12 ^c
No of events	0	0	16	24	not available
<u>Serious pneumonia</u>					
Rate	0.74	1.10	0.95	0.55	0.84 ^b
No of events	4	14	142	361	not available
<u>Fatal infection</u>					
Rate	0.18	0.32	0.17	0.14	0.24 ^d
No of events	1	4	25	89	not available

a=Rate of serious infections in TNF-antagonist-treated RA patients in British BSRBR registry
 b=Rate of opportunistic infections in a cohort of 24530 RA patients in Pharmetrics insurance claims database
 c=Rate of tuberculosis in TNF-antagonist-treated RA patients in Swedish ARTIS registry
 d=Rate of fatal infections in TNF-antagonist-treated RA patients in Spanish BIOBADASER registry

Source: Table 75 of Summary of Clinical Safety

Malignancy

Most observational studies have found an increased risk of malignancies associated with RA, with an overall relative risk of 0.7 to 2.7, a 1.1 to 5.0 relative risk of lymphoma, and a 1.1 to 1.5 relative risk for Non-Melanoma Skin Cancer (NMSC).² Published incidence rates of malignancy, excluding NMSC, in RA patients treated with biologics, have been reported in the range of 0.38 to 1.3 per 100 PY. A summary of the overall rate of malignancies, including NMSC may be found in Table 5 below. The incidence of malignancy was higher in TCZ-treated patients compared to controls, though it is difficult to draw definitive conclusions from this because control group patients were exposed for a relatively short time and malignancies would be expected to occur with longer latency. Additionally, the difference in rates between the TCZ and control group was greatest in the DMARD-IR patients compared to the overall

² Lopez-Olivo et al, JAMA 2012; 308(9):898-908

RA population. This difference appeared to be driven primarily by a lower rate of occurrence in the placebo control group of the DMARD-IR studies.

Table 5: Rate of Malignancy per 100 Patient Years, by Analysis Population

	Data in TCZ-Treated Patients				
	Controlled Data				Epidemiol. Data
	Placebo	All TCZ	LTE Studies	Post-marketing	
All malignancies, including Non-Melanoma Skin Cancer (NMSC)					
DMARD-IR Population					
PY Exposure	543	1268	14994	65099	3805 ^a
No of events	5	20	243	201	34 patients
Rate	0.92	1.58	1.62	0.31	0.89 ^a
95% CI	(0.30, 2.15)	(0.96, 2.44)	(1.42, 1.84)	(0.27, 0.35)	(0.62, 1.25)
All RA Population					
PY Exposure	743	1560			
No of events	11	25			
Rate	1.48	1.60			
95% CI	(0.74, 2.65)	(1.04, 2.37)			

^a=Based on meta-analysis of 18 clinical trials in TNF antagonist treated RA patients

Source: Table 89 of Summary of Clinical Safety

Applicant analyses of medically confirmed (via adjudication) malignancy events in the LTE showed that the most commonly reported confirmed cases—65 of 194 (33%)—were of NMSC. The pattern of malignancy otherwise also mirrored the pattern that might be expected in the underlying population, with lung cancer being the most common, followed by breast, prostate, and colon cancer. The rates and types of malignancy remain generally consistent with previously submitted data for tocilizumab.

GI Perforations

The exposure-adjusted incidence of GI perforations does not appear to be increasing with increasing exposure to TCZ treatment. The current rates are consistent with previous submissions, and the incidence is well below that observed with corticosteroids (0.39 per 100 patient-years). The estimated incidence for TNF inhibitors ranges from 0.13 per 100 patient-years to 0.15 per 100 patient-years depending on the database and analysis. The vast majority of perforations have been colonic perforations, and specifically, diverticular perforations.

Table 6: Rate of Serious GI Perforations per 100 Patient Years, by Analysis Population

	Data in TCZ-Treated Patients				
	Controlled Data				Epidemiol. Data
	Placebo	All TCZ	LTE Studies	Post-marketing	
PY Exposure	543	1268	14994	65099	56027
All serious GI perforations					
No of events	0	2	30	96	85 ^c
Rate	-	0.16 ^a	0.20 ^a	0.15 ^a	0.15 ^b
95% CI	-	(0.02, 0.57)	(0.13, 0.29)	(0.12, 0.18)	(0.12, 0.19)

^a=Medically confirmed events

^b=MarketScan healthcare claims database analysis

^c=Number of patients

Source: Table 52 of Summary of Clinical Safety

Cardiovascular Events

Thus far, there continues to be no clear safety signal with respect to lipid parameter elevations resulting in cardiovascular adverse events. As mentioned in the original BLA review, the background rate of myocardial infarction (MI) events in RA has been reported to be 0.5 to 0.8 events per 100 patient-years³. The exposure-adjusted incidences of MI events at the time of the complete response submission, and in the present submission, are summarized in Table 7 below. The rate of MI events over time has remained below published background rates for RA patients and appears to be generally stable.

Similarly, the rate of cerebrovascular accidents (stroke) has remained within published background rates in RA patients and has not increased over time. Reported background rates for RA patients range from 0.1 to 0.8 events per 100 patient-years⁴. The exposure-adjusted incidence of stroke in the TCZ development program has remained consistent over time at 0.16 events per 100 patient-years.

Table 7: Rate of Serious Cardiovascular Events per 100 Patient Years, by Analysis Population

	Data in TCZ-Treated Patients				
	Controlled Data				Epidemiol. Data
	Placebo	All TCZ	LTE Studies	Post-marketing	
PY Exposure	543	1268	14994	65099	56027 ^a
<u>Myocardial Infarction</u>					
No of events	2	3	38	59	348
Rate	0.37	0.24	0.25	0.09	0.63
95% CI	(0.04, 1.33)	(0.05, 0.69)	(0.18, 0.35)	(0.07, 0.12)	(0.57, 0.70) ^{a,d}
<u>Stroke^b</u>					
No of events	1	6	37	96	360
Rate	0.18	0.47	0.25	0.15	0.65
95% CI	(0.00, 1.03)	(0.17, 1.03)	(0.17, 0.34)	(0.12, 0.18)	(0.59, 0.73) ^a
<u>Cardiac death</u>					
No of events	1	1	20	46	7
Rate	0.18	0.08	0.13	0.07	0.24
95% CI	(0.00, 1.03)	(0.00, 0.44)	(0.08, 0.21)	(0.05, 0.09)	(0.10, 0.50) ^c

a=MarketScan healthcare claims database analysis

b=Ischemic and hemorrhagic stroke combined (excluding transient ischemic attacks)

c=Mortality rate from cardiovascular disease causes in TNF-antagonist-treated RA patients in Spanish registry

d=MI in MarketScan analysis includes all codes for acute MI, including asymptomatic MI diagnosed on testing

Source: Table 59 of Summary of Clinical Safety

Keeping in mind the limitations of the data used for the background rate comparisons, the current data are reassuring, pending more definitive data to be obtained from the cardiovascular outcomes study being performed as a postmarketing requirement.

Demyelinating Disorders

No serious demyelinating disorders were reported in the placebo controlled studies. As shown in Table 8 below, these disorders continue to be reported rarely and do not appear to be increasing with increasing exposure to TCZ.

³ Arthritis, Rheumatism and Aging Medical Information Systems (ARAMIS) database, National Data Bank for Rheumatic Diseases database

⁴ RA patients in Nurses' Health Study and in UK General Practice Research database

Table 8: Rate of Serious Demyelination Events per 100 Patient Years, by Analysis Population

	LTE Studies	Postmarketing Data
PY Exposure	14994	65099
No. events	3	7
Rate	0.02	0.01
95% CI	(0.00, 0.06)	(0.00, 0.02)

Source: Table 88 of Summary of Clinical Safety

Anaphylaxis

Anaphylaxis and hypersensitivity events have occurred throughout the TCZ clinical development program at an infrequent rate, and no events had been fatal. On approval, the USPI contained a warning about hypersensitivity and anaphylaxis. After the first post-marketing report of fatal anaphylaxis (which occurred in a patient who had hypersensitivity manifestations at a previous infusion, but received pre-medication with the next, ultimately fatal, infusion) the Warning in the USPI was updated with details of this case, and a contraindication was added for patients with known hypersensitivity to tocilizumab. Since then, an additional case of fatal anaphylaxis has been reported. In both these cases, symptoms began within 10 minutes or less after the start of infusion. The applicant has proposed further labeling changes in accordance with more than one fatal case being reported. These labeling changes will be discussed in Section 12 below.

Table 9: Rate of Anaphylaxis and Clinically Significant Hypersensitivity Events per 100 Patient Years, By Analysis Population

	Data in TCZ-Treated Patients				
	Controlled Data				Epidemiol. Data
	Placebo	All TCZ	LTE Studies	Post-marketing	
PY Exposure	543	1268	14994	65099	
<u>Anaphylaxis</u>					No relevant rates available
No of events	0	3	9 ^b	67 ^a	
Rate	-	0.24	0.06	0.10	
95% CI	-	(0.05, 0.69)	(0.03, 0.11)	(0.08, 0.13)	
<u>Clinically significant hypersensitivity AE</u>					
No of events	1	16	54	NA	
Rate	0.18	1.26	0.36		
95% CI	(0.00, 1.03)	(0.72, 2.05)	(0.27, 0.47)		

NA: Not available

a=Based on the MedDRA anaphylaxis SMQ narrow plus the preferred term of "hypersensitivity." Upon medical review, 58 of the 67 events in 65 patients reported as anaphylaxis were deemed consistent with anaphylaxis.

b=Based on the MedDRA anaphylaxis SMQ narrow plus a checkbox for hypersensitivity events occurring within 24 hours. Upon medical review, 8 of the 9 events reported as anaphylaxis were deemed consistent with anaphylaxis. By Sampson's criteria, 11 patients would be reported, for a rate of 0.07 per 100 patient-years.

Source: Tables 70 and 72 of the Summary of Clinical Safety

Discontinuations due to Adverse Events

The most common adverse events leading to discontinuation during the placebo-controlled studies were actually laboratory abnormalities, due to protocol-specified discontinuation

criteria. Otherwise, the pattern of adverse events resulting in discontinuation mirrored the pattern of events comprising serious adverse events.

Laboratory abnormalities

Tocilizumab treatment has consistent and demonstrated effects on hepatobiliary, hematologic, and lipid laboratory parameters. These abnormalities have previously been described and explored in detail in previous reviews for BLA 125276. The data in this submission are consistent with previously described effects of tocilizumab on these laboratory parameters. To summarize briefly:

1) Hepatobiliary abnormalities

Consistent with its mechanism of action (IL6 inhibition via binding of cell surface IL6 receptors), tocilizumab treatment is associated with reversible elevation in hepatobiliary parameters. Hepatocytes express high levels of IL6 receptor, and IL6 drives hepatic production of acute phase reactants. In clinical trials, approximately 50% of patients treated with tocilizumab experienced elevations in AST or ALT up to 3 times the upper limit of normal (ULN). A small percentage (1 to 7%) of patients experienced elevations from 3 to 5 x ULN, and yet smaller proportions (1 to 2%) experienced elevations from 5 to 8 x ULN. These abnormalities were reversible with discontinuation of treatment. No serious clinical hepatic events were associated with these changes in the placebo-controlled clinical studies. In the LTE and postmarketing experience, there have been relatively few cases of serious hepatic events (0.04 to 0.06 events per 100 PY), and the event rate was consistent with data from the MarketScan database for patients receiving TNF inhibitors (0.07 events per 100 PY).

2) Hematologic abnormalities

IL6 is an essential hematopoietic growth factor; therefore its inhibition can result in reduction in white blood cells and platelets. Up to 20% of patients treated with tocilizumab experience Grade 1 or Grade 2 neutropenia, however few experience more severe neutropenia. Neutropenia is typically reversible with discontinuation of TCZ. In post-marketing (estimated exposure of 65099 PY), the reporting rate of neutropenia has been approximately 0.15 events per 100 patient years (95% CI 0.12, 0.19). Of the 90 patients with a reported event of neutropenia, 13 patients also experienced one or more serious infections before or after experiencing neutropenia, and two of these patients died from infection.

Similarly, mild thrombocytopenia associated with tocilizumab treatment is not uncommon (approximately 10-15% incidence), but has been associated with relatively few clinical adverse events and is reversible with discontinuation of treatment. In the postmarketing experience (65009 PY), the reporting rate of serious thrombocytopenia events in patients treated with TCZ was estimated to be 0.07 events per 100 PY (95% CI 0.05, 0.10). Of the 47 patients reported, in two cases were reported in conjunction with disseminated intravascular coagulation and one patient experienced purpura. Details of these cases (e.g., temporal relationship to thrombocytopenia and TCZ treatment) are not known. There was otherwise no clear association with thrombocytopenia and subsequent bleeding events.

3) Lipid abnormalities

TCZ treatment has been associated with an increase in all lipid parameters—average increases of 30 mg/dl in total cholesterol, 20 mg/dl in LDL, 5 mg/dl in HDL, and 30-40 mg/dl in triglycerides. In general, LDL increases take place by Week 6 and do not increase further with successive TCZ treatment over time. These increases are reversible with discontinuation, and are also amenable to treatment with lipid-lowering agents. The rates of cardiovascular adverse events in the TCZ clinical development program remain well within published background rates in RA (see special safety concern section below). Nonetheless, with tocilizumab's approval, a controlled cardiovascular outcomes study has been enacted as a postmarketing requirement in order to attempt to more definitively describe the effect that these lipid abnormalities may have on patients receiving tocilizumab long-term. The final protocol for this study was submitted in January 2011, and the study is ongoing, with an estimated duration of 5 years to accrue sufficient events for analysis.

- **Immunogenicity**

A total of 3945 of the 4009 patients in the LTE all-exposure population were screened for anti-TCZ antibodies at any timepoint. Forty-four of the 3945 patients (1.1%) tested positive in screening and confirmation assays for anti-TCZ antibodies. Five of the 44 (11%) of these anti-TCZ antibody positive patients experienced an anaphylactic reaction. This is a higher incidence than in the antibody negative patients, suggesting immunogenicity is associated with an increased risk of anaphylaxis. In contrast, there did not appear to be a relationship between a positive result for neutralizing antibodies and loss of efficacy. In additional analyses provided in this submission, patients who missed 2 or more consecutive doses of TCZ did not appear to have an increased rate of immunogenicity compared to those who did not.

- **Special safety concerns**

Eighteen months after approval, reviewers in the Office of Surveillance and Epidemiology (OSE) performed a review of the post-marketing safety profile of TCZ, as mandated by the Food and Drug Administration Amendments Act (FDAAA) of 2007. As a result of this review, OSE identified four safety issues for which additional information was requested of the applicant: pancreatitis, pancytopenia, convulsions, and interstitial lung disease. A summary of incidence rates may be found in Table 10, below. Because these are infrequent events that are spontaneously observed in the RA patient population, it is difficult to identify good estimates of background incidence as context and difficult to draw conclusions about relative risk attributable to TCZ treatment.

Table 10: Rate of Serious Pancreatitis, Pancytopenia, Convulsions, and Interstitial Lung Disease per 100 Patient Years, by Analysis Population

	Data in TCZ-Treated Patients				
	Controlled DMARD-IR Data				
	Placebo	All TCZ	LTE Studies	Post-marketing	Epidemiol. Data
PY exposure	543	1268	14994	65099	3032
Serious Pancreatitis					
No of events	0	1	16	28	213
Rate	-	0.08	0.11	0.04	0.26 ^a
(95% CI)		NC	(0.06, 0.17)	(0.03, 0.060)	(0.22, 0.29)
Pancytopenia					
No of events	0	0	8	24	NA
Rate	-	-	0.05	0.04	0.01 ^b
(95% CI)			(0.02, 0.11)	(0.02, 0.05)	
Convulsions					
No of events	0	2	16	23	NA
Rate	-	0.16	0.11	0.04	0.02 to 0.03 ^b
(95% CI)		NC	(0.05, 0.17)	(0.02, 0.05)	
Interstitial Lung Disease					
No of events	1	4	88	102	NA
Rate	0.18	0.32	0.59	0.16	0.1 to 1.2 ^c
(95% CI)	(0.00, 1.03)	(0.09, 0.81)	(0.47, 0.72)	(0.13, 0.19)	

NA=Not Available; NC = Not Calculated

a=Incidence of pancreatitis in RA patients calculated from published data on 213 cases over 84143 PY of follow-up

b=Reporting rate in FDA Adverse Event Reporting System (AERS) database, per 100 exposed patients in all approved indications

c=Published incidence of ILD in RA patients treated with biological DMARDs

Source: Table 32 of Summary of Clinical Safety

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

Dr. Hull has concluded that the types and rates of adverse events submitted with this supplement are generally consistent with those reviewed with the original BLA and subsequent supplements and has not identified any new safety signals.

- **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)**

Notable issues are described above.

9. Advisory Committee Meeting

No Advisory Committee Meeting was convened for this efficacy supplement. A meeting of the Arthritis Advisory Committee was convened on July 29, 2008 to discuss the clinical data in the original tocilizumab BLA submission.

10. Pediatrics

The pediatric assessment and plan for tocilizumab for polyarticular juvenile idiopathic arthritis (PJIA) were reviewed by the Pediatric Review Committee (PeRC) as part of the original BLA and was re-evaluated in the setting of this supplement due to the proposed expansion of the indication. With the original BLA submission, the applicant requested a deferral for patients age 2-17 with PJIA, and a waiver for children 0-2, since PJIA is extremely rare in this age group. These requests were granted with the original approval action for the tocilizumab BLA and were again discussed by the PeRC on August 22, 2012. PeRC agreed that the original waiver and deferral are still applicable for this supplement. In any case, the PREA PMR study in PJIA patients has already been conducted under a Special Protocol Assessment agreement and has been completed. (b) (4)

(b) (4) In addition, the applicant obtained orphan designation for the PJIA indication in July 2012.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—Not applicable.
- **Exclusivity or patent issues of concern**—No issues.
- **Financial disclosures**—Acceptable.
- **Other GCP issues**—Not applicable.
- **DSI audits**—No inspections/audits were requested with this supplement, as the efficacy data were evaluated in the context of the original BLA submission.
- **Other discipline consults**—None requested.
- **Any other outstanding regulatory issues**—None identified.

12. Labeling

- **Proprietary name**—No issues, already approved.
- **Important issues raised by OPDP and OSE**
- **Physician labeling**

The following issues require revision prior to approval of the prescribing information (PI):

1) The applicant amended the indication to remove the TNF-inhibitor inadequate responder descriptor, (b) (4) “who have had inadequate response to one or more DMARDs.” (b) (4)

(b) (4) Due to its potent immunosuppressive effects, Dr. Hull and I believe that the TCZ indication should limit its use to second-line therapy, after failure of one or more DMARDs.

2) The additional language proposed by the applicant for the Hypersensitivity and Anaphylaxis Warning was generally acceptable, [REDACTED] (b) (4) in the Warning, as it reinforces the concept that anyone demonstrating hypersensitivity should not be re-challenged with additional doses of TCZ, as premedication may not be helpful.

The applicant accepted all revisions requested by the review team.

- **Carton and immediate container labels (if problems are noted)**—No issues.
- **Patient labeling/Medication guide (if considered or required)**—The Medication Guide and REMS materials should be revised to be consistent with the PI changes.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval of this efficacy supplement to expand the indicated population to patients who have had inadequate response to one or more DMARDs, contingent on agreement on final labeling and REMS material modifications.

- **Risk Benefit Assessment**

The risk-benefit profile of tocilizumab treatment remains favorable based on the data in this submission.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies (REMS)**

The currently approved REMS for Actemra consists of a communication plan. Modifications to the communication plan materials were recommended by DRISK to make these materials consistent with the prescribing information changes.

- **Recommendation for other Postmarketing Requirements and Commitments**

No additional postmarketing requirements or commitments are recommended on the basis of the data in this submission.

- **Recommended Comments to Applicant**

None.

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/s/

SARAH K YIM
09/22/2012