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APPLICATION NUMBER:
BLA 125276/S049

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental BLA
Application Number(s)	125276/49
Priority or Standard	Standard
Submit Date(s)	December 13, 2011
Received Date(s)	December 13, 2011
PDUFA Goal Date	October 12, 2012
Division / Office	DPARP/ODE2
Reviewer Name(s)	Keith M Hull, MD, PhD
Review Completion Date	September 7, 2012
Established Name	Tocilizumab
(Proposed) Trade Name	Actemra
Therapeutic Class	anti-Interleukin-6 receptor mAb
Applicant	Hoffmann-LaRoche
Formulation(s)	Intravenous
Dosing Regimen	4 or 8 mg/kg every 4 weeks
Indication(s)	Rheumatoid Arthritis
Intended Population(s)	Moderately to Severely Active RA

Template Version: [March 6, 2009](#)

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	10
2.1	Product Information	10
2.2	Tables of Currently Available Treatments for Proposed Indications	10
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues With Consideration to Related Drugs.....	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	12
3	ETHICS AND GOOD CLINICAL PRACTICES.....	17
3.1	Submission Quality and Integrity	17
3.2	Compliance with Good Clinical Practices	17
3.3	Financial Disclosures.....	17
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	18
4.1	Chemistry Manufacturing and Controls	18
4.2	Clinical Microbiology.....	18
4.3	Preclinical Pharmacology/Toxicology	18
4.4	Clinical Pharmacology.....	18
4.4.1	Mechanism of Action.....	18
4.4.2	Pharmacodynamics.....	18
4.4.3	Pharmacokinetics.....	18
5	SOURCES OF CLINICAL DATA.....	19
5.1	Studies/Clinical Trials	19
6	REVIEW OF EFFICACY	23
	Efficacy Summary.....	23
6.1	Indication.....	23
6.1.1	Methods	23
6.1.2	Demographics.....	23
6.1.3	Patient Disposition	23
6.1.4	Analysis of Primary Endpoint(s).....	23
6.1.4.1	Clinical Response in DMARD-IR Patients.....	23
6.1.4.2	Radiographic Response in DMARD-IR Patients	25
6.1.4.3	Physical Function in DMARD-IR Patients	25
6.1.5	Analysis of Secondary Endpoints(s)	26
6.1.6	Other Endpoints	26
6.1.7	Subpopulations	26

6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	26
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	26
7	REVIEW OF SAFETY.....	27
	Safety Summary	27
7.1	Methods.....	27
7.2	Adequacy of Safety Assessments	29
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	30
7.2.1.1	Extent of Exposure	30
7.2.1.2	Demographics and Baseline Disease Characteristics	32
7.3	Major Safety Results	33
7.3.1	Deaths.....	33
7.3.2	Nonfatal Serious Adverse Events	37
7.3.3	Dropouts and/or Discontinuations	40
7.3.4	Significant Adverse Events	40
7.3.4.1	Serious Hepatic Events and Increases in Transaminase and Bilirubin Levels....	40
7.3.4.2	Gastrointestinal Perforations	44
7.3.4.3	Serious Cardiovascular Events	47
7.3.4.4	Hypersensitivity and Anaphylaxis.....	50
7.3.4.5	Serious Infections.....	52
7.3.4.6	Serious Bleeding Events and Thrombocytopenia	58
7.3.4.7	Demyelination Events	60
7.3.5	Submission of Specific Safety Concerns.....	61
7.3.5.1	Pancreatitis	61
7.3.5.2	Pancytopenia	62
7.3.5.3	Convulsions.....	63
7.3.5.4	Interstitial Lung Disease	64
7.3.5.5	Malignancies	66
7.7	Additional Submissions/Safety Issues	68
7.7.1	4-Month Safety Update	68
8	POSTMARKET EXPERIENCE.....	72
9	APPENDICES	73
9.1	Literature Review/References	73
9.2	Labeling Recommendations	73
9.3	Advisory Committee Meeting.....	73

Table of Tables

Table 1. Approved Biologic Products for Treatment of RA in the United States.....	11
Table 2. Approved Non-Biologic DMARDs for Treatment of RA in the United States ...	11
Table 3. Regulatory Actions for Tocilizumab	13
Table 4. Proportion of Patients with no Progression of Total Sharp-Genant Score from Baseline to Week 52 and Week 54	25
Table 5. Rates of Death/100 PY during Placebo-Controlled Studies (Pooled Patient Population).....	34
Table 6. Deaths Occuring in the Long-Term Extension Studies between February 11, 2010 and April 1, 2011	35
Table 7. Rate of Deaths/100 PY During Long-Term Extension Studies	36
Table 8. Primary Causes of Deaths During the Long-Term Extension Studies	36
Table 9. Rate of SAE/100 PY During the Placebo-Controlled Studies (Pooled Patient Population).....	38
Table 10. ALT and AST Shifts from Normal at Baseline to Worst Post-Baseline Value During Long-Term Extension Studies	42
Table 11. Rate of Adjudicated GI Perforations/100 PY During the Placebo-Controlled Studies	45
Table 12. Rates of Serious Infections (Pooled Patient Population)	53
Table 13. Site-Specific SIRs showing Statistically Significant SIR>1 for the LTE Population	67

Table of Figures

Figure 1. Proportion of DMARD-IR Patients Achieving ACR20, ACR50, and ACR70 Responses at Week 24	24
Figure 2. Rate of SAEs by 12-Month Periods for the Long-Term Extension Population	39
Figure 3. Rate of ALT and AST Elevations >ULN to 3 x ULN Over Time During the Long-Term Extension Studies.....	42
Figure 4. Rate of Serious Infections/100PY by 12-Month Periods During the Long-Term Extension Studies.	54

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Recommended approval with revisions to the proposed labeling to support expansion of the indication as follows:

- Actemra is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to [REDACTED] (b) (4)

1.2 Risk Benefit Assessment

Tocilizumab (TCZ) is the first-in-class recombinant human monoclonal antibody targeting the interleukin-6 receptor (IL-6R). Tocilizumab selectively binds to soluble and membrane-bound human IL-6Rs thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6.

The US FDA originally approved TCZ on January 08, 2010 for the treatment of patients with moderate-to-severe rheumatoid arthritis (RA) after demonstrating clinical benefit on the American College of Rheumatology (ACR) response rates for signs and symptoms of the disease. On January 4, 2011, TCZ was granted the additional claims of inhibition of radiographic progression, improvement in physical function, and major clinical response.

The current submission provides additional safety data to support expansion of the indication from *“the treatment of patients with moderately to severely active RA who have had an inadequate response to tumor necrosis factor (TNF) antagonists”* to *“the treatment of patients with moderately to severely active RA who have had an inadequate response to [REDACTED]”* (b) (4)

Summary of Efficacy Data

The efficacy data demonstrating the clinical benefit to patients with RA have been previously submitted and reviewed in prior submissions. No new or additional efficacy data were submitted with the current application; however, a brief summary of the previously submitted efficacy data with special consideration to the DMARD inadequate responders (DMARD-IR) population was performed. Full review of the efficacy of TCZ in adult patients with RA, including the efficacy of TCZ in TNF-IR patients and TCZ monotherapy, can be found in the submissions of BLAs 125276/0, 7, 10, and 11.

Three well-controlled Phase 3 studies (WA17822, WA17823, WA18063) enrolling RA patients who were DMARD-IR provided the efficacy data demonstrating that TCZ-treated patients showed a clinically meaningful improvement in signs and symptoms of their disease compared to patients receiving placebo. A higher proportion of TCZ-

treated patients achieved ACR20, ACR50, and ACR70 responses at Week 24 compared to placebo-treated patients. A significantly higher proportion of patients treated with TCZ 8 mg/kg + MTX reported a DAS28 score <2.6 (demonstrating very low disease activity) at Week 52 compared to patients randomized to the placebo + MTX control arm, 47% vs. 8% (respectively). A higher proportion of patients treated with either TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX achieved a major clinical response (ACR70 response for a continuous 24-week period) compared to patients treated with placebo + MTX (4% and 8% vs. 0.5%, respectively).

Study WA17823 was designed to assess the progression of radiographic structural damage at Week 52 using the total Sharp-Genant scoring method in RA patients treated with TCZ or placebo. At Week 52, patients treated with TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX had significantly lower mean changes in total Sharp-Genant scores than patients treated with placebo + MTX, 0.33 ± 1.3 , 0.25 ± 0.98 , and 1.17 ± 3.14 , respectively. Additionally, a greater proportion of TCZ treated patients had not progression of total Sharp-Genant scores from baseline to Week 52 and Week 104. Together these data show that TCZ + MTX-treated patients have less radiographic progression at one and two years compared to patients treated with placebo + MTX.

In addition to assessing radiographic damage, Study WA17823 assessed physical function and disability using the Health Assessment Questionnaire Disability Index (HAQ-DI). Changes in HAQ-DI of >0.22 u have been shown to be clinically meaningful with regards to improvement of physical functions. At the Week 52 endpoint, a greater proportion of patients treated with TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX had statistically significant changes ≥ 0.3 u in the HAQ-DI compared to placebo + MTX-treated patients, 60% and 63% vs. 53%, respectively.

Summary of Safety Data

The safety data used to support the change in indication are derived from three main sources of the TCZ development program:

- Placebo-controlled randomized studies
- Long-term extension (LTE) clinical studies
- Postmarketing data from the sponsor's global safety database

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-IR patients were enrolled in study WA18062, and study WA17824 enrolled patients who were MTX-naïve. Cumulative TCZ safety data from the LTE studies are included up to April 1, 2011 and provides an additional 14 months of long-term safety data compared to what was previously submitted in the sponsor's previous sBLA. This corresponds to an additional 2700 PYs duration of exposure analysis. A total of 4009 patients who received at least one dose of TCZ are included in the LTE all-exposure population. Postmarketing safety data from the sponsor's global safety database of TCZ-treated patients recorded through July 29, 2011, forms the majority of the data to support the

safety profile of TCZ. A total of 5,403 SAEs were reported in the postmarketing database. Based on the global sales data and the sponsor-supplied postmarketing trials, the total PYs of exposure to TCZ calculated for the postmarketing event rate analyses was 65,099 PY.

Three main areas of safety concern were specifically addressed in this submission: elevated liver enzymes leading to potential serious hepatic injury, elevated low density lipoprotein (LDL) concentrations leading to cardiovascular (CV) events, and gastrointestinal (GI) perforations.

The estimated rate of serious hepatic events in TCZ-treated patients during the postmarketing period was at least 0.06 events/100 PY, which was consistent with the rate observed in the LTE population (0.04 events/100 PY) and estimated rate of RA patients treated with TNF antagonists (0.07 events/100 PY). Similar to previous finding, the majority of patients experienced serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations to the upper limit of normal (ULN) following the first dose of TCZ. This elevation in transaminases tended to remain stable with subsequent doses of TCZ and only a small proportion of patients had AST or ALT levels $>5 \times$ ULN (1% and 3%, respectively). There was no trend for an increased risk of transaminase levels increasing over time. Also, there was no clear relationship between elevations in aminotransferases or bilirubin leading to serious hepatic events. Overall, these data do not demonstrate an increased risk of TCZ-treated patients developing a serious hepatic event greater than what was already known from previously submitted data and is similar to what is observed in TNF antagonist-treated patients.

In the postmarketing experience, the estimated rate of serious myocardial infarctions (MI; 0.09 events/100 PY), serious stroke (0.15 events/100 PY), and cardiac deaths (0.07 events/100 PY) among TCZ-treated patients were consistent with the rates reported previously in the LTE population (0.3 events/100 PY; 0.3 events/100 PY, and 0.1 events/100 PY, respectively) and the rates estimated for RA patients treated with TNF antagonists. As noted in previous reviews, lipid and triglyceride levels increased after initiation of TCZ in a proportion of patients but remained stable thereafter. Overall, the data submitted to date are consistent with previous data and do not support a direct link between TCZ-induced increases of LDL and triglyceride concentrations and increases in CV events at this time.

The reporting rates of GI perforations in the postmarketing setting (0.23 events/100 PY) was similar to the rate of GI perforations reported in the LTE population (0.2 events/100 PY) and the rates reported in the MarketScan database and literature for RA patients treated with TNF antagonists (0.18 events/100 PY). Although the rate of GI perforations in the TCZ-treated patients appears to be similar to patients treated with TNF antagonists, there appears to be an increased rate compared to patients not treated with TCZ as evidenced by the data observed in the placebo-controlled studies. These data are consistent with the previous data.

Overall, the additional safety data provided in this submission were consistent with the original BLA and no new safety signals were identified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Tocilizumab currently has a REMS consisting of a Medication Guide and Communication Plan. Based on this submission, I believe the current REMS remains adequate.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on this submission, I do not have specific recommendations for additional post-marketing requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Tocilizumab (is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the 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. The data obtained from in vitro assays demonstrate that tocilizumab has essentially no or minimal complement dependent cytotoxicity (CDC) activity and little or no significant antibody dependent cellular cytotoxicity (ADCC) activity. The molecular mass of the protein moiety of the antibody is approximately 145 kDa. The tocilizumab drug product comes in 80 mg, 200 mg, and 400 mg vials at 20 mg/mL concentration. All three strengths are a sterile, colorless to pale yellow, preservative-free liquid and are identical in qualitative and quantitative composition (dose-proportional), differing only with respect to fill volume (4 ml, 10 ml, and 20 ml, respectively). The concentrate is to be diluted to 100 mL in 0.9% sodium chloride solution for intravenous infusion prior to administration. Administration is as a single intravenous drip infusion over 1 hour.

Tocilizumab is the first in class (targeting IL-6 signaling pathway) biologic agent approved in the United States for the treatment of:

- Rheumatoid Arthritis: Adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies.
- Systemic Juvenile Idiopathic Arthritis: Patients 5 years of age and older with active systemic juvenile idiopathic arthritis.

The purpose of the current submission is to provide updated clinical and postmarketing safety data to support expansion of the current RA indication to (b) (4) with moderately to severely active RA. No new or additional efficacy data have been provided with the current submission.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 lists the currently available approved biologic treatments for RA. These include the five currently approved TNF inhibitors (infliximab, etanercept, and adalimumab, golimumab, and certolizumab pegol), one IL-1 antagonist (anakinra), one B-cell depleting therapy (rituximab, an anti-CD20 monoclonal antibody), and one T-cell costimulation modulator (abatacept, a CTLA4-Ig fusion protein).

Table 1. Approved Biologic Products for Treatment of RA in the United States

Product	BLA (Sponsor)	Year Approved for RA ¹	Molecular Characteristics	Route of Administration
Etanercept (ENBREL)	103795 (Immunex)	1998	Fusion Protein (TNF antagonist)	SC
Infliximab (REMICADE)	103772 (Centocor)	1999	Monoclonal Ab (TNF antagonist)	IV
Anakinra (KINERET)	103950 (Amgen)	2001	Fusion Protein (IL-1 antagonist)	SC
Adalimumab (HUMIRA)	125057 (Abbott)	2002	Monoclonal Ab (TNF Antagonist)	SC
Abatacept (ORENCIA)	125118 (Bristol-Myers Squibb)	2005	Fusion Protein (T-cell modulator)	IV/SC
Rituximab (RITUXAN)	103705 (Genentech/Biogen Idec)	2006	Monoclonal Ab (anti-CD20/B-cell depleting agent)	IV
Golimumab (SIMPONI)	125289 (Centocor)	2009	Monoclonal Ab (TNF antagonist)	SC
Certolizumab Pegol (CIMZIA)	125160 (UCB)	2009	Fab fragment (TNF antagonist)	SC
Tocilizumab (ACTEMRA)	125276 (Roche)	2010	Monoclonal Ab (IL-6 receptor antagonist)	IV

¹Infliximab was initially approved in 1998 for treatment of Crohn's Disease and rituximab was initially approved in 1997 for non-Hodgkin's lymphoma.

Table 2 lists the non-biologic DMARDs which are currently approved for RA in the US.

Table 2. Approved Non-Biologic DMARDs for Treatment of RA in the United States

Product ¹	NDA (Sponsor)	Year Approval ²
Sulfasalazine (AZULFIDINE)	7-073 (Pfizer)	1998
Methotrexate (METHOTREXATE)	8-085 (PO) 11-719 (IV) (Multiple)	1999
Hydroxychloroquine (PLAQUENIL)	9-768 (Sanofi-Aventis)	2001
Prednisone	Multiple (Multiple)	2002
Azathioprine (IMURAN)	16-324 (Prometheus Labs)	2005
Penicillamine (CUPRIMINE)	19-853 (Aton)	2006
Auranofin (RIDAURA)	18-689 (Prometheus Labs)	2009
Cyclosporine (NEORAL/SANDIMMUNE)	50-715 50-625 (Novartis)	2009
Leflunomide (ARAVA)	20-905 (Sanofi-Aventis)	2010

¹Alternative formulations (e.g., solutions) are not included in this table. Corticosteroids and NSAIDs are approved for reduction of the signs and symptoms of RA but are not included in this table. ²Initial approval may not have been for RA.

2.3 Availability of Proposed Active Ingredient in the United States

Tocilizumab is commercially available in the United States since it received FDA approval on January 8, 2010.

2.4 Important Safety Issues With Consideration to Related Drugs

Tocilizumab is the first in class IL-6 signaling inhibitor. Therefore, the safety profile of IL-6 inhibition is based on the information submitted in the original the supplemental BLA, and anticipated effects based on currently available knowledge about the biological effects of IL-6 and the clinical trial experience with tocilizumab. Based on this information, the primary issues of concern pertain to:

- Overall immunosuppression and the risk for serious infection.
- Liver enzyme abnormalities and concern that this could result in clinically meaningful hepatotoxicity.
- Reduction in white blood cell counts and the potential risk for infection.
- Reduction in platelet counts and the potential for serious bleeding events.
- Elevated lipids with potential long-term ramifications of cardiovascular risk. As IL-6 is the primary driver of acute phase reactants, and inflammation is associated with increased cardiovascular risk, it is also possible that inhibition of IL-6 may be beneficial with respect to cardiovascular risk.
- Potential promotional effect on certain malignancies as suggested by basic science literature; however, the clinical trial evidence to date suggests that tocilizumab treatment does not have an impact on the rates of malignancy.
- Gastro-intestinal perforations have been identified as a potential safety signal in the clinical development program and are prospectively monitored by the applicant and reported as part of the Periodic Adverse Event Reporting.

The supplemental BLA safety data submitted to date indicates an overall tocilizumab safety profile consistent with that reviewed in the original BLA. No new safety signals have been identified.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An overview of the important regulatory interactions pertaining to the current submission is shown in Table 3.

Table 3. Regulatory Actions for Tocilizumab

Date	Interaction
November 19, 2007	Original BLA 125276/0 submission for RA
March 28, 2008	4-month safety update for BLA 125276/0
September 17, 2008	CR letter from FDA for BLA 125276/0
July 8, 2009	CR submission for BLA 125276/0
January 5, 2010	Pre-action teleconference meeting
January 8, 2010	Approval letter for BLA 1252756/0
March 9, 2010	Summary Basis of Approval for BLA 125276/0
March 16, 2010	sBLA 125276/7, 10, 11 submission for progression of structural damage, major clinical response, physical function.
June 28, 2010	4-month safety update for sBLA 125276/7, 10, 11. Teleconference discussing sBLA for expanding indication to DMARD-IR population.
July 29, 2010	Post-action meeting to discuss proposed analysis plan and overall approach for present submission to extend indication to include DMARD-IR patients
October 14, 2010	sBLA 125276/22 submission for sJIA
January 4, 2011	Approval letter for sBLA 125276/7, 10, 11
January 26, 2011	3-month safety update for sBLA 125276/22
April 15, 2011	Approval letter for sBLA 125276/22
September 29, 2011	Written feedback from FDA on proposed format and content of current submission
November 14, 2011	Pre-sBLA meeting
BLA=Biologics License Application; RA=Rheumatoid Arthritis; CR=Complete Response; sBLA=Supplemental Biologics License Application; sJIA=Systemic Juvenile Idiopathic Arthritis	

The original BLA for TCZ in 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. The clinical efficacy data submitted in the original BLA were derived from 5 randomized, double-blind, controlled trials of TCZ in 4211 RA patients with moderately to severely active disease. Three of the studies (WA17822, WA17823, and WA18063) enrolled patients with an inadequate response to at least one non-biologic DMARD (DMARD-IR; e.g., MTX), study WA18062 evaluated TCZ in patients with an inadequate response to TNF antagonists (TNF-IR), and study WA17824 evaluated TCZ in patients who were MTX-naïve. These data provided substantial evidence of the efficacy of TCZ for the treatment of RA. The safety data submitted included approximately 4700 patients and over 7900 patient-years (PY) of exposure in the global safety database and analyses were consistent with the profile of an immunosuppressant, namely an increased risk of serious infections. Likely as a function of its mechanism of action, TCZ treatment also resulted in abnormalities of laboratory parameters, including decreased white blood cell count, increases in lipid levels, and liver enzyme elevations, although these were not associated with serious clinical adverse events in the controlled setting of the clinical trial experience. Malignancies, GI perforations, and demyelinating adverse events were also 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. Overall, the risk-benefit profile of TCZ in RA appeared to be favorable based on these clinical data.

A meeting of the Arthritis Advisory Committee (AAC) was convened on July 29, 2008 to discuss the clinical data in the original tocilizumab BLA submission. The members of the committee concurred that efficacy was demonstrated in RA. They were uncertain whether the data clearly indicated a benefit of 8 mg/kg over the 4 mg/kg dose in patients with an inadequate response to DMARDs, as some members noted that the components of the ACR response criteria showed little difference between doses with the exception of effect on C-reactive protein (CRP) levels. The risk of serious infection was considered to be similar to that seen with commonly used agents in RA. GI perforation and demyelination adverse events were noted in light of their relative rarity, and the risks of these were not felt to outweigh the potential benefits observed with TCZ treatment. The main area under discussion was the potential risk conferred by the elevation in LDL levels. Some members expressed great concern while other members were reassured by the lack of a signal for clinical cardiovascular events and by the potentially beneficial anti-inflammatory effects of tocilizumab on cardiovascular risk. The committee voted 10-to-1 in favor of approval.

Taking into account the AAC discussion and the overall safety concerns, the Agency notified the sponsor on January 5, 2010, 3 days prior to issuing the action letter, that given the availability of other effective therapies on the market for the treatment of RA, TCZ would initially be restricted to the TNF-IR population of RA patients. The Agency further advised at that time that the potential safety concerns associated with TCZ would need to be evaluated in the postmarketing setting prior to expanding the indication for TCZ to include DMARD-IR patients. The Agency requested the sponsor to submit such data at a time when the postmarketing safety database was large enough for signal detection of rare and serious toxicities and to identify the total PY of exposure to TCZ necessary to improve confidence in the safety profile of TCZ in the postmarketing setting for increases in hepatic enzymes leading to serious hepatic injury, increases in LDL leading to potential CV events, and GI perforations. The current submission is in response to the Agency's request.

On January 08, 2010 a regulatory action to approve tocilizumab was taken. The Approval Letter outlined requirements specific to the tocilizumab program based on the review of the available safety data. These requirements include:

1. Risk Evaluation and Mitigation Strategies (REMS) under to ensure that the benefits of the drug outweigh the risks. The REMS consists of a Medication Guide, Communication Plan, and a timetable for submission of assessments of the REMS.
2. Post-marketing requirements (PMR):
 - Pregnancy registry to evaluate pregnancy outcomes for women exposed to Actemra (tocilizumab) during pregnancy. Utilize the established Organization of Teratology Information Specialists (OTIS) pregnancy registry to evaluate pregnancy outcomes.

- Long-term, observational study of patients who continue to be treated with tocilizumab in the open-label part of the treatment trials WA18695 and WA18696 to evaluate long-term serious risks of Actemra and to accrue safety data on at least 1000-1500 patients treated for 5 years.
- A randomized, controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with tocilizumab, e.g., stroke, non-fatal MI, cardiovascular death.
- A randomized trial to study the effects of TCZ on therapeutic vaccines. B cell-dependent antigens (e.g., pneumococcal polysaccharide vaccine) and T cell-dependent antigens (e.g., tetanus toxoid) will be evaluated.
-

On March 16, 2010, the applicant submitted supplements 7, 10, and 11 to the BLA, providing additional clinical safety and efficacy data to support the additional claims of inhibition of radiographic progression of structural damage, improvements of physical function, and major clinical response.

To address the Agency's concerns regarding the safety of TCZ in the DMARD-IR patient population, the sponsor presented a proposal for analyses of postmarketing data based on ~64,000 PY of TCZ exposure from global postmarketing studies. Additionally, the sponsor proposed evaluating the AE rate of TNF antagonists as a comparator using information from existing healthcare databases. During a teleconference on June 28, 2010, the Agency agreed that the proposed analysis plan was reasonable and would be adequate to support a filing for the use of TCZ in DMARD-IR patients. The Agency also requested further safety analyses including deaths, serious adverse events (SAE), serious infections, malignancies, and AE rates in DMARD-IR patients from the controlled periods of the RA studies.

Final agreements regarding the content of the current filing were ultimately reached following a pre-sBLA meeting on November 14, 2011. Major agreements included:

- 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
- Use of the Thomson Reuters MarketScan Healthcare databases for generating event rates in RA patients treated with TNF antagonists
- The safety data and analyses as proposed were acceptable to assess potential risks associated with TCZ treatment regarding increases in serum hepatic aminotransferase levels, increases in LDL cholesterol, and GI perforations
- The data package to evaluate additional AEs in the DMARD-IR population was sufficient
- The rationale to include patients that escaped therapy within the death analysis of the control periods of the RA studies and to provide a sensitivity analysis excluding escaped patients

- The proposal for the sponsor to provide narratives for malignancy and serious infection events from the global safety database as part of the 4-month safety update
- The proposal to outline descriptive safety analyses plan and relevant laboratory information for:
 - Interstitial lung disease
 - Pancreatitis
 - Convulsions
 - Pancytopenia/bone marrow failure

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The supplemental BLA submission was in electronic common technical document (eCTD) format and was adequately organized. The coding dictionary used for mapping investigator verbatim terms to preferred terms provided was adequate.

Inspections by the Division of Scientific Investigations (DSI) were conducted as part of the original BLA review. No significant data integrity issues were identified and no new DSI inspections were deemed necessary for the review of this supplemental BLA.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in the supplemental BLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 11,972 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

DSI inspection conducted at the time of the original BLA review revealed no violations pertaining to compliance with GCP.

3.3 Financial Disclosures

The applicant submitted FDA Form 3454 (v.10/09) certifying investigators and their spouses/dependents were in compliance with 21 CFR part 54 in previous submissions. No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No significant efficacy/safety issues have been identified by the other review disciplines.

4.2 Clinical Microbiology

No new clinical microbiology data were submitted with this supplement for review.

4.3 Preclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data were submitted with this supplement for review.

4.4 Clinical Pharmacology

No new clinical pharmacology data were submitted with this supplement for review

4.4.1 Mechanism of Action

No new data on the mechanism of action were submitted with the current supplement for review. As previously reviewed, IL-6 is a pleiotropic cytokine that has important roles in the regulation of the immune response, inflammation, and hematopoiesis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of RA. Tocilizumab selectively binds to soluble and membrane-bound human IL-6 receptors, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent signaling cascade of IL-6.

4.4.2 Pharmacodynamics

No new data regarding pharmacodynamics were submitted with the current supplement for review.

4.4.3 Pharmacokinetics

No new data regarding pharmacokinetics were submitted with the current supplement for review.

5 Sources of Clinical Data

5.1 Studies/Clinical Trials

The purpose of the current submission is to provide updated clinical and postmarketing safety data to support expansion of the current RA indication to (b) (4) with moderately to severely active RA. No new or additional efficacy data have been provided with the current submission.

The current safety review is based upon four main sources of data:

- Placebo-controlled randomized studies
- Long-term extension clinical studies
- Postmarketing data from the sponsor's global safety database
- Epidemiologic data of background AE rates in RA patients treated with TNF antagonists

Details regarding the individual study designs, endpoints, treatment regimens, and statistical testing can be found in the clinical reviews of previous submissions.

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-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 patient 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. Although this same safety data was analyzed in previous submissions, the current pooling by patient population allows for a more thorough analysis for specifically comparing the DMARD-IR population to the placebo-controlled patients where needed.

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 what was previously submitted in the sponsor's previous sBLA. This corresponds to an additional 2700 PYs duration of exposure 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. All data are included from the time of first dose TCZ, thus AEs occurring during the placebo-controlled periods are also included in the analyses of the LTE all exposure

population. A total of 4009 patients who received at least one dose of TCZ are included in the LTE all-exposure population.

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. A total of 5,403 SAEs were reported in the postmarketing database. Of these, 46% were from spontaneous reports, 31% were reported via the JPMS, and 24% reported from the unblinded and open-labeled studies.

In general, postmarketing databases are typically associated with underreporting of spontaneous safety reports; however, since TCZ has only been marketed for several years (since 2008 in Japan and 2010 in the US), the degree of underreporting is likely to be less than that associated with a drug marketed for a longer period of time¹.

The TCZ JPMS program for RA was started following the approval of TCZ by the Japanese Health Authority on April 6, 2008. The program consisted of two studies. The first study enrolled 8,527 RA patients who were followed up to a minimum of 28 weeks. Approximately 5,000 of these patients were subsequently enrolled in a second long-term follow-up study where fatal, malignant, serious infection, cardiac, and GI perforation AEs are being followed for up to 3 years. An interim JPMS report containing data on 3,881 patients was submitted to the Agency on December 17, 2009 and has been reviewed previously.

Calculation of Minimum PY Exposure to TCZ for Postmarketing Safety Database

As previously agreed to with the Agency, the sponsor calculated the minimum amount of TCZ exposure needed to provide 90% probability that the lower bound of the confidence interval (CI) of the TCZ rate of AEs (serious hepatic events, serious CV events, and GI perforations) was greater than the background rate for RA patients treated with TNF antagonists assuming the observed TCZ rate was 1.5 times the background rate (based on a Poisson distribution). The background rates and CIs were based on the rates and CIs for patients with RA treated with TNF antagonists followed in the US-based healthcare MarketScan database (0.01, 0.14, and 1.74 for serious hepatic events, GI perforations, and serious CV events, respectively). In general, the background AE rates were similar between the claims data analysis used for the sample size calculation and the MarketScan analysis.

Based on the sponsor's sample size calculations, 63,913 PY of TCZ exposure was required to detect an increase of 1.5 times the background rate for serious hepatic events in TCZ-treated patients. Similarly, 45,653 PY and 2,744 PY were required to

¹ Hartnell NR and Wilson JP. Replication of the Weber effect using postmarketing adverse events reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy*. 2004; 24:743-49.

detect an increase of 1.5 times the background rate for GI perforations and serious CV events, respectively. A total of 65,099 PY of TCZ exposure are used for the current analyses of safety in the postmarketing safety database allowing for the detection of an increased risk of 1.4 times the background rate for GI perforation, 1.1 times the background rate of CV events, 1.2 times the background rate for MI and stroke. Sensitivity analyses demonstrated that the reporting rate of serious hepatic events did not change using more conservative assumptions for the rest of world (ROW) region for average body weight, number of doses per year, and average TCZ dose.

Overall, the sponsor's calculated minimum exposure rates are considered adequate to assess that overlapping CIs are not an effect of too few AEs or too small an exposed patient population.

MarketScan Healthcare Claims Database Analysis

To provide a better frame of reference regarding the rate of TCZ-associated AEs, the Agency agreed with the sponsor that it would be helpful to compare to the AE rates in RA patients treated with TNF-antagonists. To this end, the sponsor performed a retrospective cohort analysis of the US-based Thomson Reuters MarketScan healthcare claims database. Specifically, the incidence rates of serious hepatic events, serious GI perforations, serious CV events, and malignancies in patients treated with TNF antagonists.

The data were obtained from the Thomson Reuters MarketScan Commercial Claims and Encounters Database using ICD 9 codes. The primary cohort was identified using patients with at least two claims for RA between 30 and 365 days apart, who were 18 years of age or older at the time of their first RA claim. Overall, the MarketScan database analysis was based on > (b) (4) PY of exposure from (b) (4) RA patients treated with TNF antagonists. The median follow-up of TNF antagonist exposure was approximately 3 years in duration.

While this data is useful, claims data have several limitations because the claims are collected for the purpose of reimbursement for health services and not for safety outcomes. The presence of a diagnosis code does not always indicate positive presence of disease. To further increase specificity in the outcome identification, the sponsor required their defined cohort to have a hospitalization for all outcome events, except for malignancies which may be treated in the outpatient setting.

Other Epidemiological Data Sources

Background AE rates not included in the MarketScan analysis were obtained from published scientific data. Standardized mortality ratios (SMR) using expected mortality rates in the general US population were based on the US National Vital Statistics Reports. Standardized Incidence Ratio (SIR) analysis for malignancies using expected cancer rates in the US Surveillance and Epidemiology End Results (SEER) program based on the general US population.

Clinical Review
Keith M Hull, MD, PhD

sBLA 125276/49
Actemra[®]/tocilizumab for RA

Overall, the quantity and quality of the safety data presented in the current submission is adequate to assess the relative risk-benefit ratio of TCZ-treated RA patients who are DMARD-IR.

6 Review of Efficacy

Efficacy Summary

The current submission is aimed at assessing the safety profile of TCZ using updated data from the LTE studies and postmarketing experience. The efficacy data presented here have been previously submitted and reviewed in the original submission and no new or additional efficacy data were submitted with the current application. A brief summary of the previously submitted efficacy data will be reviewed in this section with special consideration to the DMARD-IR population. Full review of the efficacy of TCZ in adult patients with RA, including the efficacy of TCZ in TNF-IR patients and TCZ monotherapy, can be found in the submissions of BLAs 125276/0, 7, 10, and 11.

6.1 Indication

The purpose of the current submission is to provide updated clinical and postmarketing safety data to support expansion of the current RA indication to (b) (4) with moderately to severely active RA, i.e., patients with RA who have had an inadequate response to (b) (4).

6.1.1 Methods

A brief summary of the previously submitted efficacy data will be reviewed in this section with special consideration to the DMARD-IR population. Full review of the efficacy of TCZ in adult patients with RA, including the efficacy of TCZ in TNF-IR patients and TCZ monotherapy, can be found in the submissions of BLA 125276/0 and sBLAs 125276/ 7,10,11.

6.1.2 Demographics

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

6.1.3 Patient Disposition

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

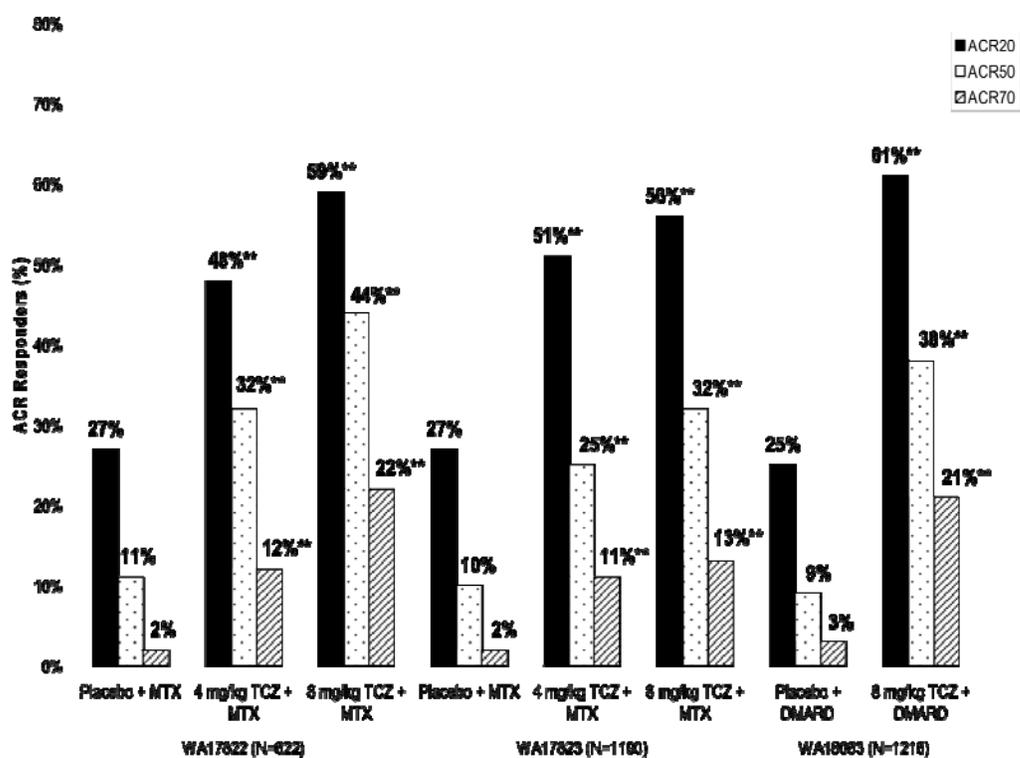
6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Clinical Response in DMARD-IR Patients

Three well-controlled Phase 3 studies (WA17822, WA17823, WA18063) enrolling RA patients who were DMARD-IR provided the efficacy data demonstrating that TCZ-treated patients showed a clinically meaningful improvement in signs and symptoms of their disease compared to patients receiving placebo.

A higher proportion of TCZ-treated patients achieved ACR20, ACR50, and ACR70 responses at Week 24 compared to placebo-treated patients (Figure 1). A significantly higher proportion of patients treated with TCZ 8 mg/kg + MTX reported a DAS28 score <2.6 (demonstrating very low disease activity) at Week 52 compared to patients randomized to the placebo + MTX control arm, 47% vs. 8% (respectively). A higher proportion of patients treated with either TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX achieved a major clinical response (ACR70 response for a continuous 24-week period) compared to patients treated with placebo + MTX (4% and 8% vs. 0.5%, respectively).

Figure 1. Proportion of DMARD-IR Patients Achieving ACR20, ACR50, and ACR70 Responses at Week 24



ITT population: intent-to-treat population. Patients who escaped or withdrew were considered non-responders.

* p < 0.01, TCZ + MTX/DMARD vs placebo + MTX/DMARD.

** p < 0.0001, TCZ + MTX/DMARD vs placebo + MTX/DMARD.

*** Adapted from sponsor's Clinical Overview: Figure 2, page 25.

6.1.4.2 Radiographic Response in DMARD-IR Patients

Additional data provided in sBLAs 125276/7, 10, 11 demonstrated clinically meaningful improvements regarding inhibition of structural damage and improvement of physical function in patients with RA.

Study WA17823 was designed to assess the progression of radiographic structural damage at Week 52 using the total Sharp-Genant scoring method in RA patients treated with TCZ or placebo. At Week 52, patients treated with TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX had significantly lower mean changes in total Sharp-Genant scores than patients treated with placebo + MTX, 0.33 ± 1.3 , 0.25 ± 0.98 , and 1.17 ± 3.14 , respectively. Additionally, a greater proportion of TCZ treated patients had not progression of total Sharp-Genant scores from baseline to Week 52 and Week 104 (Table 4). Together these data show that TCZ + MTX-treated patients have less radiographic progression at one and two years compared to patients treated with placebo + MTX.

Table 4. Proportion of Patients with no Progression of Total Sharp-Genant Score from Baseline to Week 52 and Week 54

Patient Visit	Placebo + MTX	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + MTX
Week 52			
n	290	339	348
Non-progressors (%)	195 (67%)	273 (81%)	294 (85%)
Week 104			
n	294	343	353
Non-progressors (%)	195 (66%)	256 (75%)	292 (83%)

Data collected after withdrawal or on escape therapy are excluded. Missing data from Weeks 52 and 104 are imputed using linear extrapolation. Analysis based on logistic regression and adjusted for region. Table adapted from sponsor's Clinical Overview, Table 3, page 26

*Adapted from sponsor's Clinical Overview: Table 3, page 26.

6.1.4.3. Physical Function in DMARD-IR Patients

In addition to assessing radiographic damage, Study WA17823 assessed physical function and disability using the Health Assessment Questionnaire Disability Index (HAQ-DI). Changes in HAQ-DI of >0.22 u have been shown to be clinically meaningful with regards to improvement of physical functions. At the Week 52 endpoint, a greater proportion of patients treated with TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX had statistically significant changes ≥ 0.3 u in the HAQ-DI compared to placebo + MTX-treated patients, 60% and 63% vs. 53%, respectively.

6.1.5 Analysis of Secondary Endpoints(s)

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

6.1.6 Other Endpoints

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

6.1.7 Subpopulations

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Data previously reviewed in submission BLA 125276/0 and sBLAs 125276/7,10,11.

7 Review of Safety

Safety Summary

7.1 Methods

The nature of this submission is to provide an updated assessment of the safety profile of TCZ in patients with RA based on TCZ postmarketing and clinical studies data as well as epidemiologic background event rates reported with RA patients using TNF antagonists. Thus, the current safety review is an extension of the analyses reviewed in the previous submissions. As such, terminology and definitions of exposure, patient populations, etc are consistent with previous submissions.

The submission contains clinical safety data on AEs, SAEs, and AEs of special interest. The applicant has used the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.1 for assigning preferred terms to AEs, diseases, and surgical and medical procedures for this Summary of Clinical Safety and the 4-month Safety Update. To account for duration of exposure, the applicant has presented AE rates as a function of total patient-years of observation (i.e., duration on trial treatment) and expressed as rates of events per 100 patient-years. This analysis provides useful information that allows for comparison of AEs over time.

Abnormal laboratory data were classified according to the common toxicity criteria (CTC) grading system (version 3) as well as sponsor-defined marked abnormality criteria, based on the International Standard for the Handling and Reporting of Laboratory Data. Lipid data were classified according to the National Cholesterol Education Program Adult Treatment Panel III guidelines. Each vital sign parameter (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate and temperature) was summarized using descriptive statistics.

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-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 patient 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. Although this same safety data was analyzed in previous submissions, the current pooling by patient population allows for a more thorough analysis for specifically comparing the DMARD-IR population to the placebo-controlled patients where needed.

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 what was previously submitted in the sponsor's previous sBLA. This corresponds to an additional 2700 PYs duration of exposure 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. All data are included from the time of first dose TCZ, thus AEs occurring during the placebo-controlled periods are also included in the analyses of the LTE all exposure population. A total of 4009 patients who received at least one dose of TCZ are included in the LTE all-exposure population

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. A total of 5,403 SAEs were reported in the postmarketing database. Of these, 46% were from spontaneous reports, 31% were reported via the JPMS, and 24% reported from the unblinded and open-labeled studies.

In general, postmarketing databases are typically associated with underreporting of spontaneous safety reports; however, since TCZ has only been marketed for several years (since 2008 in Japan and 2010 in the US), the degree of underreporting is likely to be less than that associated with a drug marketed for a longer period of time².

The TCZ JPMS program for RA was started following the approval of TCZ by the Japanese Health Authority on April 6, 2008. The program consisted of two studies. The first study enrolled 8,527 RA patients who were followed up to a minimum of 28 weeks. Approximately 5,000 of these patients were subsequently enrolled in a second long-term follow-up study where fatal, malignant, serious infection, cardiac, and GI perforation AEs are being followed for up to 3 years. An interim JPMS report containing data on 3,881 patients was submitted to the Agency on December 17, 2009 and has been reviewed previously.

2 Hartnell NR and Wilson JP. Replication of the Weber effect using postmarketing adverse events reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy*. 2004; 24:743-49.

MarketScan Healthcare Claims Database Analysis

To provide a better frame of reference regarding the rate of TCZ-associated AEs, the Agency agreed with the sponsor that it would be helpful to compare to the AE rates in RA patients treated with TNF-antagonists. To this end, the sponsor performed a retrospective cohort analysis of the US-based Thomson Reuters MarketScan healthcare claims database. Specifically, the incidence rates of serious hepatic events, serious GI perforations, serious CV events, and malignancies in patients treated with TNF antagonists.

The data were obtained from the Thomson Reuters MarketScan Commercial Claims and Encounters Database using ICD 9 codes. The primary cohort was identified using patients with at least two claims for RA between 30 and 365 days apart, who were 18 years of age or older at the time of their first RA claim. Overall, the MarketScan database analysis was based on > (b) (4) PY of exposure from (b) (4) RA patients treated with TNF antagonists. The median follow-up of TNF antagonist exposure was approximately 3 years in duration.

While this data is useful, claims data have several limitations because the claims are collected for the purpose of reimbursement for health services and not for safety outcomes. The presence of a diagnosis code does not always indicate positive presence of disease. To further increase specificity in the outcome identification, the sponsor required their defined cohort to have a hospitalization for all outcome events, except for malignancies which may be treated in the outpatient setting.

Other Epidemiological Data Sources

Background AE rates not included in the MarketScan analysis were obtained from published scientific data. Standardized mortality ratios (SMR) using expected mortality rates in the general US population were based on the US National Vital Statistics Reports. Standardized Incidence Ratio (SIR) analysis for malignancies using expected cancer rates in the US Surveillance and Epidemiology End Results (SEER) program based on the general US population.

Overall, the quantity and quality of the safety data presented in the current submission are adequate to assess the relative risk-benefit ratio of TCZ-treated RA patients who are DMARD-IR.

7.2 Adequacy of Safety Assessments

The pooled safety database provides for a large clinical experience of exposure in the RA population exposed to TCZ. The placebo-controlled studies enrolled 4098 patients and provides for comparison to placebo-matched controls. The LTE studies are comprised of 4009 patients who received at least one dose of TCZ and are continued to accrue data in the long-term extensions studies. The LTE population has approximately 14,994 PY of exposure. The postmarketing global safety database of TCZ-treated patients contains data recorded through July 29, 2011 and accounts for a total of 65,099 PY of TCZ exposure are used for the current analyses of safety in the postmarketing

safety database. The 4-month safety update accounts for an additional 9,193 PY of exposure. On the whole, the quality and quantity of the safety data submitted are adequate to assess the risks associated with TCZ therapy.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Extent of Exposure

For the placebo-controlled and LTE populations, exposure was measured as follows:

- Extent of Exposure=number of patients actually receiving infusions plus up to 28 days post infusion (excludes missing doses).
- Duration in study=date of last safety observation minus the date of the first dose plus one. Time on escape therapy is excluded for the placebo-controlled populations analyses except for deaths.

The measures of exposure are reported in PY.

Placebo-Controlled Studies

Of the 4,098 patients who received study drug during the placebo-controlled periods of the Phase 3 studies, 2,644 patients received TCZ and 1454 patients received placebo. The total PY duration across all placebo-controlled populations was 1,560 PY for TCZ-treated patients and 743 PY for the corresponding placebo-treated patients (Table). Of the total PY of study drug exposure, DMARD-IR patients accounted for 1,268 PY of TCZ exposure and 542 PY for placebo/MTX/DMARD exposure.

The total exposure to TCZ across all placebo-controlled populations was 1,441 PY and 679 PY for exposure to placebo. The DMARD-IR population accounted for 1180 PY of TCZ exposure and 501 PY to placebo exposure.

Long-Term Extension Studies

There was a total of 14,994 PY of duration, the majority of which was from DMARD-IRs (Table). 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.

The total exposure to TCZ during the LTE study population was 13503 PY. 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

Assumptions used to estimate the average TCZ doses were based on market research conducted in each of the different regions. Based on this data, the following assumptions were made in the three different regions:

- ROW
 - Average body weight: 72 kg
 - Average TCZ dose: 7.2 mg
 - 80% of patients receiving 8 mg/kg
 - 20% of patients receiving 4 mg/kg
 - Average number of TCZ doses per year: (b) (4) treatments
 - Average annual dose per patient per year: (b) (4)

- US/Canada
 - Average body weight: 72 kg
 - Average TCZ dose: 6.4 mg
 - 60% of patients receiving 8 mg/kg
 - 40% of patients receiving 4 mg/kg
 - Average number of TCZ doses per year: (b) (4) treatments
 - Average annual dose per patient per year: (b) (4)

- Japan
 - Average body weight: 53 kg
 - Average TCZ dose: 7.7 mg
 - Incorporates dose adjustments and compliance to treatment
 - Average number of TCZ doses per year: (b) (4) treatments
 - Average annual dose per patient per year: (b) (4)

The total PYs of exposure to TCZ was calculated from global sales data and exposure data from the sponsor's postmarketing studies. Global sales data was generated based on the number of commercial vials of TCZ sold for use outside of clinical trials and vials used in postmarketing clinical studies through July 29, 2011. Exposure data from the sponsor's postmarketing studies was separate from the calculated global sales, as these studies did not use commercially available product. Total exposure for these patients was calculated as the total number of infusions per trial per 28 days per year. Based on the global sales data and the sponsor-supplied postmarketing trials, the 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. Sensitivity analyses (data not shown) using differing assumptions were performed and the estimate and 95% CI did not change suggesting that the sponsor's assumptions and calculated patient exposure to TCZ is adequate to conduct the current safety analyses on which this review is based.

As agreed to with the Agency, the sponsor estimated exposure from global sales data using a series of assumptions including average weight of patients, average frequency of TCZ dosing, and average dose. Countries were grouped into three main regions: ROW, USA/Canada, and Japan. Exposure calculations for the ROW and USA/Canada are based on similar assumptions except for average dose due to differences between the regions in the approved TCZ starting dose (8 mg/kg vs. 4 mg/kg). Japan was treated as a distinct region due to the comprehensive data collected in the JPMS program. The assumptions used for generating PY of exposure were based on data

from clinical trials and market research conducted in Europe and the US, while assumptions for Japan are based on the data from the JPMS program in RA patients.

(b) (4)

Due to limitations in the postmarketing safety database, estimates of individual patient exposure were simulated using SAS version 8.2. The number of patients receiving TCZ therapy that needed to be “enrolled” to achieve the required exposure was estimated by trial and error using the simulation algorithm. Since the sales data are provided as an annual figure, estimated “enrollment” followed a uniform distribution annually in the simulations. The length of time the patients remained on TCZ was assumed to follow an exponential distribution and the dropout rate within the first year was assumed to be 30% with subsequent years 10%. Based on the results of 1,000 iterations, the average number of patients required to achieve 65,099 PYs exposure was approximately 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.

MarketScan Healthcare Claims Database Analysis

A total of (b) (4) patients with RA were included in the MarketScan healthcare database with a median duration of follow-up of approximately 3 years. Of these patients, (b) (4) were identified as receiving treatment with a TNF antagonist and also had a median duration of follow-up of approximately 3 years duration.

7.2.1.2 Demographics and Baseline Disease Characteristics

Placebo-Controlled Clinical Studies

The demographics and baseline disease characteristics of patients enrolled in the placebo-controlled periods of the Phase 3 studies have been reviewed in the original submission (BLA 125276/0). For all studies, patients were typical of the US population of patients with RA and individual treatment arms were well balanced with regards to demographic and baseline RA characteristics, including range of disease duration, prior/concomitant treatments, and comorbidities. The median age was 50 to 55 years with comparable degrees of disease activity as evidenced by mean DAS28 scores of approximately 6.5. Greater than 80% of patients were receiving concomitant MTX at the time of study entry, while the remaining 20% of patients were receiving other non-biologic DMARDs alone or in combination with MTX. As previously concluded, the demographics and baseline disease characteristics are typical of the US RA population and the treatment arms were well balanced.

Long-Term Extension Studies

The demographic characteristics of the three populations of patients enrolled in the LTE studies were generally comparable. The majority of patients were white females with a median age of 51-54 years. This population is representative of the US patient population with RA. All populations had moderately to severely active RA as evidenced by DAS28 scores greater than 6.3. Differences in disease duration were as expected based on the nature of the study with MTX-naïve patients having a median disease duration of 1.6 years, DMARD-IR of 7 years, and TNF-IR with approximately 10 years disease duration. As previously concluded, the demographics and baseline disease characteristics are typical of the US RA population and the treatment arms were well balanced.

Postmarketing Global Safety Database

Demographic data and baseline disease characteristics of patients are not usually reported to postmarketing safety databases; however, the data that was available is consistent with what is expected in the US population of RA patients namely, predominantly White females between 50 and 60 years of age. This data is generally comparable to patients from the other sources of safety data and are representative of the US RA patient population.

MarketScan Healthcare Claims Database

Of the (b) (4) patients treated with a TNF antagonist in the MarketScan healthcare claims database, over 70% were female with an average age of 57 years. Further demographic data and disease baseline characteristics were not available.

7.3 Major Safety Results

7.3.1 Deaths

Placebo-Controlled Studies

A total of 15 patients died during the placebo-controlled periods of the Phase 3 clinical studies (Table 5). Eleven patients were from the DMARD-IR population, two patients from the MTX-naïve population, and two patients from the MTX-NR population. Ten of the 15 deaths were reported for TCZ-treated patients. All deaths were previously reported and reviewed in previous submissions.

Table 5. Rates of Death/100 PY during Placebo-Controlled Studies (Pooled Patient Population)

	PBO + DMARD (n=1010)	TCZ+DMARD (n=806)	TCZ+MTX (n=1633)
DMARD-IR			
Number of Deaths	4	6	1
Exposure (PY)	543	966	530
Deaths/100 PY (95% CI)	0.74 (0.2, 1.9)	0.62 (0.2, 1.4)	0.19 (0, 1.1)
MTX-Naive	PBO + MTX (n=190)	TCZ 8 mg/kg (n=200)	-
Number of Deaths	0	2	-
Exposure (PY)	92	101	-
Deaths/100 PY (95% CI)	-	2 (0.2, 7.2)	-
			-
MTX-NR	PBO + MTX (n=94)	TCZ 8 mg/kg (n=99)	-
Number of Deaths	1	1	-
Exposure (PY)	46	49	-
Deaths/100 PY (95% CI)	2.2 (0.1, 12.1)	2(0.1, 11.4)	-

*Adapted from sponsor's Clinical Safety Summary: Table 25, page 95.

As shown in Table 5, the death rate/100 PY for TCZ-treated patients was similar to that of placebo-treated patients. Two of the DMARD-IR deaths occurred while the patients were on escape therapy and their PY duration on TCZ was excluded from the rate calculation; however, sensitivity analysis demonstrated that this did not impact the calculated death rate. Overall, the death rate/100 PY was similar between TCZ-treated DMARD-IR compared to placebo-treated DMARD-IR patients.

Long-Term Extension Studies

A total of 85 patient deaths have been reported through April 1, 2011 for the LTE population including the ten TCZ-treated patients who died during the placebo-controlled period of the studies and 16 patients who died since the last safety update of February 17, 2010. Causes of death for the 16 newly reported deaths are outlined in Table 6, and are similar in nature to the reasons reported and reviewed in previous submissions.

Table 6. Deaths Occuring in the Long-Term Extension Studies between February 11, 2010 and April 1, 2011

Patient Population Patient Number	Cause of Death	Day of Death after TCZ Treatment
DMARD-IR		
46633/3620	Myocardial Infarction	1582
46680/2242	Cerebrovascular Accident	1796
50981/7154	Hemorrhagic Stroke	1685
46594/3266	Bronchopneumonia	1718
46687/1105	Neuroendocrine Carcinoma	1896
46723/2296	Acute Hepatic Failure	1374
46786/2328	Enteritis	1214
46790/2310	Death-Unspecified	1040
46806/2495	Splenic Rupture	1661
50843/7399	Pancreatic Carcinoma	1853
50935/6084	Pneumonia	2017
50985/7559	Hepatic Neoplasm	1309
TNF-IR		
56992/5248	Bronchopneumonia	1459
MTX-naïve		
51176/4320	Small Cell Lung Carcinoma	1651
64051/4582	Pneumonia	1565
85913/9004	Sudden Death	1289

*Adapted from sponsor's Clinical Safety Summary: Table 27, page 97.

As shown in Table 7, the death rate/100 PY in the LTE periods were similar between the DMARD-IR, TNF-IR, and MTX-naïve patient populations. A summary of the primary causes of death by System Organ Class (SOC) for the 85 deaths are shown in Table 8. The most frequently reported primary causes of death in the LTE population were infections, cardiovascular events, and malignancies. Pneumonia accounted for 10 of the 24 cases reported for infectious etiologies responsible for deaths, followed by nine cases of sepsis, two cases of endocarditis, and one case each of a CNS infection, gastrointestinal infection, and one atypical infection of blastomyces pneumonia. Of the 15 cardiac-related deaths, 11 cases were attributed myocardial infarction, two cases of cardiac failure, and one case each of cardiomyopathy and ventricular tachycardia. There were an additional five cardiovascular-related deaths reported in the Nervous System Disorders SOC with three cases of strokes and one case of subarachnoid hemorrhage. Of the reported 14 cases of Neoplasms, all were malignant with 4 cases of lung cancer, and one case each of breast, colon, esophageal, glioblastoma, hepatic, gastric, neuroendocrine, pancreatic, and spindle cell carcinoma. The remainder of the deaths was notable for 4 cases of pulmonary embolism, 2 cases of multi-organ failure, and 2 cases of suicide. All other reported causes of death occurred single events.

Table 7. Rate of Deaths/100 PY During Long-Term Extension Studies

	DMARD-IR (n=2904)	TNF-IR (n=464)	MTX-naive (n=417)	All TCZ* (n=4009)
Number of Deaths	57	13	11	85
Exposure (PY)	11126	1508	1547	14994
Deaths/100 PY (95% CI)	0.5 (0.4, 0.7)	0.9 (0.5, 1.5)	0.7 (0.4, 1.3)	0.6 (0.5, 0.7)

*Adapted from sponsor's Clinical Safety Summary: Table 28, page 98.

Table 8. Primary Causes of Deaths During the Long-Term Extension Studies

Primary Cause of Death	All TCZ (n=4009)
Total Deaths	85 (2%)
Infections and Infestations	24 (<1%)
Cardiac Disorders	15 (<1%)
Neoplasms Benign, Malignant, and Unspecified	14 (<1%)
Nervous System Disorders	7 (<1%)
Respiratory, Thoracic, and Mediastinal Disorders	7 (<1%)
General Disorders and Administration Site Conditions	6 (<1%)
Gastrointestinal Disorders	4 (<1%)
Injury, Poisoning, and Procedural Disorders	4 (<1%)
Psychiatric Disorders	2 (<1%)
Hepatobiliary Disorders	1 (<1%)
Renal and Urinary Disorders	1 (<1%)

*Adapted from sponsor's Clinical Safety Summary: Table 29, page 99.

In summary, the 16 newly reported deaths are consistent with the causes of death reported in previous submissions. The death rate/100 PY is similar between the DMARD-IR and the other treatment populations. Overall, there were no new safety signals identified in the reported patients' deaths during the LTE studies.

Postmarketing Global Safety Database

A total of 253 TCZ-treated patients were reported to have died in the postmarketing experience. Based on an estimated exposure of 65,099 PY the reporting death rate/100 PY is estimated to be approximately 0.4 (95% CI: 0.3, 0.4), similar to what was observed in the clinical trials with TCZ, the most commonly reported causes of death, by SOC, were Infections and Infestations (89 patients) and Cardiac Disorders (49 patients). It is worth noting that 49 of the patients' deaths were classified as General Disorders and Administration Site Conditions. Overall, the death rate/100 PY of TCZ-treated patients reported in the postmarketing safety database was consistent with that observed in the clinical trials with TCZ.

Mortality rates reported from large observational studies in biologic-naïve RA patients range from 3.1 to 5.2 deaths/100 PY^{3,4,5}, while the reported death rates in TNF

3 Bjornadal L, et al. J Rheumatol. 2002 May; 29(5): 906-12

4 Carmona L, et al Ann Rheum Dis. 2007 Jul; 66(7):880-5

5 Jacobsson LT, et al Ann Rheum Dis. 2007 May;66(5):670-5

antagonist-treated patients from the same studies demonstrated lower overall death rates ranging between 0.7 to 1.6 deaths/100 PY, suggesting that TNF antagonists may decrease mortality in RA patients. Sokka et al⁶ conducted a systematic review and meta-analysis of 54 RA patient cohorts reported that mortality rates were approximately 1.5 to 1.6-fold higher in RA patients compared to the general population with cardiovascular accounting for approximately 40% of the deaths in RA patients, then followed by malignancy (17%), infection (14%), respiratory disease (9%), and gastrointestinal disease (5%).

To estimate a standard mortality ratio (SMR) for TCZ-treated patients in the LTE population the sponsor derived an estimate of 99 expected deaths in the LTE population as outlined in Section. Given that 85 deaths were actually observed in the LTE population, the calculated SMR of TCZ-treated patients was 0.9 (95% CI: 0.7, 1.1) suggesting that the observed number of deaths in the LTE population was not appreciably different from the expected number in a population with similar demographic characteristics.

Taken as a whole, these data show that the deaths/100 PY estimated for the TCZ postmarketing setting was not higher than the rate observed in the clinical trials with TCZ. Moreover, the calculated death rate is similar to that observed in RA patients treated with TNF antagonists. The rate of death during the placebo-controlled studies was similar between TCZ-treated patients and patients treated with placebo. The most frequently reported causes of death for RA patients treated with TCZ were also consistent with that reported in the general RA population.

7.3.2 Nonfatal Serious Adverse Events

Placebo-Controlled Studies

Safety data regarding SAEs during the placebo-controlled periods of the Phase 3 studies have been analyzed and reviewed in previous submission for TCZ. In general, the rate of SAEs/100 PY during the placebo-controlled period of the studies tended to be highest in the TNF-IR population of patients compared to the DMARD-IR or MTX-naïve populations (Table 9). The increased rate of SAEs in the TNF-IR populations was mostly due to increased rates of infection. In fact, Infections and Infestations accounted for the majority of SAEs in all TCZ-treated populations.

6 Sokka T, et al Ann Rheum Dis. 2009 Nov;68(11):1715-20

Table 9. Rate of SAE/100 PY During the Placebo-Controlled Studies (Pooled Patient Population)

	PBO + DMARD (n=1010)	TCZ+DMARD (n=1407)	TCZ+MTX (n=611)
DMARD-IR			
Number of SAE	61	121	55
Exposure (PY)	543	841	427
SAE/100 PY (95% CI)	11.2 (8.6, 14.4)	14.4 (11.9, 17.2)	12.9 (9.7, 16.8)
TNF-IR			
	PBO + MTX (n=160)	TCZ 4 mg/kg (n=163)	TCZ 8 mg/kg (n=175)
Number of SAE	23	14	17
Exposure (PY)	62	69.9	79.6
SAE/100 PY (95% CI)	37 (23.4, 55.5)	20 (11, 33.6)	21.4 (12.4, 34.2)
MTX-naive			
	PBO + MTX (n=190)	TCZ 8 mg/kg (n=193)	-
Number of SAE	14	9	-
Exposure (PY)	15.3	9.3	-
SAE/100 PY (95% CI)	15.3 (8.4, 25.7)	9.3 (4.3, 17.7)	-

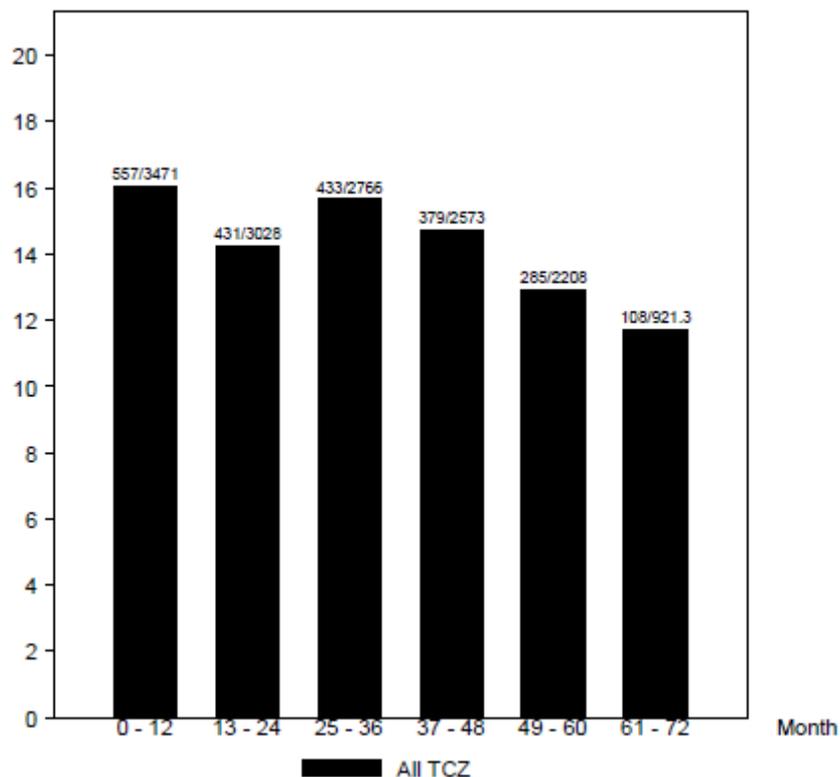
*Adapted from sponsor's Clinical Safety Summary: Table 33, page 106.

TCZ-treated patients in the DMARD-IR population had a marginally higher rate of SAE/100 PY compared to the placebo-treated patients (Table 9). After Infections and Infestations as the leading cause of SAEs in the DMARD-IR population, TCZ-treated patients, compared to placebo-treated patients, reported a higher rate of Injury, Poisoning, and Procedural Complications (1.5 events/100 PY vs. 0.7 events/100 PY, respectively), Gastrointestinal Disorders (1.3 events/100 PY vs. 0.7 events/100 PY), Neoplasms Benign, Malignant, and Unspecified (1 events/100 PY vs. 0.6 events/100 PY), Blood and Lymphatic System Disorders (0.5 events/100 PY vs. 0.2 events/100 PY) and Renal and Urinary Disorders (0.4 events/100 PY vs. 0.2 events/100 PY).

Long-Term Extension Studies

The rate of SAEs in the LTE population through April 1, 2011 was 14.6 events/100 PY (95% CI; 14, 15.3). As shown in Figure 2, the rate of SAEs did not increase over the time during the six-year observation period. The types of SAEs were consistent with those reported during the placebo-controlled studies. Infections and Infestations were the most frequently reported events at 4.5 events/100 PY while all other SOC classes were less than 1.5 events/100 PY. Overall the rate and type of SAEs were consistent with those observed in previous submissions.

Figure 2. Rate of SAEs by 12-Month Periods for the Long-Term Extension Population



Adapted from sponsor's Clinical Safety Summary: Figure 3, page 109.

As a comparison, Leombruno et al⁷ studied the safety of TNF antagonists in a meta-analysis of 18 randomized studies involving 8,808 RA patients. A total of 499 (14%) of the 3581 TNF antagonist-treated patients reported a SAE over a cumulative 3032 PY, resulting in an unadjusted incidence rate of 16.5 events/100 PY, which is consistent with the SAE rate observed in TCZ-treated patients during the LTE period.

Postmarketing Global Safety Database

A total of 5,403 SAEs were reported in the postmarketing data with approximately half being spontaneous reports. The estimated reporting rate for SAEs from the postmarketing database is estimated to be at least 8.3 events/100 PY based on the estimated postmarketing patient exposure of 65,099 PY. This number is lower than the reported rates of SAEs during the placebo-controlled and LTE periods of the studies, and likely represents an underreporting of events in the postmarketing setting. A Risk Evaluation and Mitigation Strategy (REMS) are in place to increase awareness prescriber-initiated event reporting. The types of SAEs were consistent with those reported during the placebo-controlled studies with Infections and Infestations being the most frequently reported (2.31 events/100 PY; 95% CI 2.2, 2.4).

⁷ Leombruno et al. Ann Rheum Dis. 2009 Jul;66(7):1136-45

In general, the overall reporting rates of SAE were similar in the ROW region and Japan, 8.2 events/100 PY vs. 8.4 events/100 PY, respectively. However, there were three SOC categories where the rate of SAEs were higher in the Japanese population compared to the ROW: Neoplasms, Benign, Malignant, and Unspecified (0.5 events/100 PY vs. 0.3 events/100 PY, respectively); Infections and Infestations (2.9 events/100 PY vs. 1.9 events/100 PY); and Respiratory, Thoracic, and Mediastinal Disorders 0.6 events/100 PY vs. 0.5 events/100 PY, respectively). The increased rate of neoplasms was accounted for by a higher number of reports for gastric cancer, lymphoma, and histiocytosis hematophagia; the increased rate of infections was due to a higher number of reported cases of pneumocystis jiroveci pneumonia, atypical mycobacterial infections, and bacterial pneumonia; and the increased rate of respiratory disorders was accounted for by a higher number of reported cases of interstitial lung disease and organizing pneumonia. The higher number of reported cases of these events is likely due to a combination of regional differences in the patient populations as well as a more accurate reporting of events via the JPMS reporting system.

In summary, during the postmarketing experience, the estimated rate of SAEs/100 PY for TCZ-treated patients was lower than the rate of SAE observed in the placebo-controlled and LTE studies as well as for the estimated SAE rate calculated for RA patients treated with TNF antagonists. The overall types of SAEs reported in the postmarketing dataset were consistent with the types of SAEs observed during the clinical trials of TCZ, with Infections and Infestations being the most frequently reported SAE. No new safety signals were identified.

7.3.3 Dropouts and/or Discontinuations

Patients who have dropped out or discontinued from studies are included in the current safety analysis as they relate to the identification of a safety signal; however, quantification of the dropouts/discontinuations as they relate to the overall study conduct is not included and have been reviewed in detail in previous submissions.

7.3.4 Significant Adverse Events

7.3.4.1 Serious Hepatic Events and Increases in Transaminase and Bilirubin Levels

Rheumatoid arthritis patient treated with TCZ have been observed to experience mild or moderate elevations of hepatic transaminases, namely aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The frequency of transaminase elevations is increased when used in combination with potentially hepatotoxic drugs, e.g., MTX. Analyses of serious hepatic events are based on safety reports from the dataset using MedDRA preferred terms contained in “hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions” and the “hepatitis, non-infectious” standard MedDRA Queries terms. Rates of liver enzyme abnormalities are based on preferred terms

contained in the “liver-related investigations, signs, and symptoms” for the postmarketing dataset only.

Placebo-Controlled Studies

No serious hepatic events were reported during the placebo-controlled studies. As reported in the original BLA, a single DMARD-IR patient treated with TCZ 8 mg/kg experienced a single, asymptomatic elevation of transaminases and was withdrawn due to hepatotoxicity. This event resolved completely and was not reported as an SAE.

During the placebo-controlled studies, all patient populations had an elevation of mean/median serum AST and ALT concentrations to the upper limits of normal (ULN) range following treatment with TCZ. This elevation in transaminases remained stable thereafter with continued treatment with TCZ. These results are consistent with what was reported in previous submissions for TCZ. For the DMARD-IR population, 48% of TCZ-treated patients reported an increase in transaminases or bilirubin levels from the ULN to three-times ULN. Only 5% and 2% of TCZ-treated patients from the DMARD-IR population experienced transaminase levels of 3-5x ULN and >5x ULN, respectively. More DMARD-IR patients experienced hepatic enzyme and bilirubin elevations compared with MTX-naïve patients.

Longer-Term Extension Studies

A total of six serious hepatic events were reported during the LTE studies involving four patients in the DMARD-IR population and one patient each from the MTX-naïve and MTX-NR populations. The rate of serious hepatic events in the LTE population was 0.04 events/100 PY (95% CI; 0.01, 0.09). All events, except for one, are believed to be TCZ-related. One DMARD-IR patient died due to the event, three patients discontinued from TCZ treatment, and one patient required lower doses of TCZ. All but two cases were reported in previous submissions. The newly reported cases are summarized briefly below:

- Patient 46689/2083 was a 58 year-old female receiving treatment with TCZ + MTX who underwent cholecystectomy for acute cholelithiasis and was found to have hepatic cirrhosis. Tocilizumab therapy was discontinued.
- Patient 46723/2296 was a 59 year-old female receiving treatment with TCZ who died secondary to acute hepatic failure and hepatic venous thrombosis.

A detailed review of liver biopsies were submitted as part of the sponsor’s complete response submission in July 2009 with an additional six biopsies reported in subsequent submissions. Although the liver biopsies were not required, investigators were permitted to biopsy at their discretion to evaluate hepatic enzyme elevations. An additional four biopsies have been reported in the current submission that resulted in 2 diagnoses of hepatic steatosis and one case each of cirrhosis and metastatic pancreatic cancer.

Similar to the placebo-controlled studies, mean/median transaminase levels increased within the normal range following the initiation of TCZ treatment and remained stable thereafter. A majority of patients reported an increase in ALT (2640/3689 patients;

72%) and AST (2279/3812 patients; 60%) levels from normal values at baseline to greater than the ULN at some point during the LTE studies. As shown in Table 10, the majority of patients had transaminase levels of <3 x ULN and only a small minority of patients had elevations >3 x ULN.

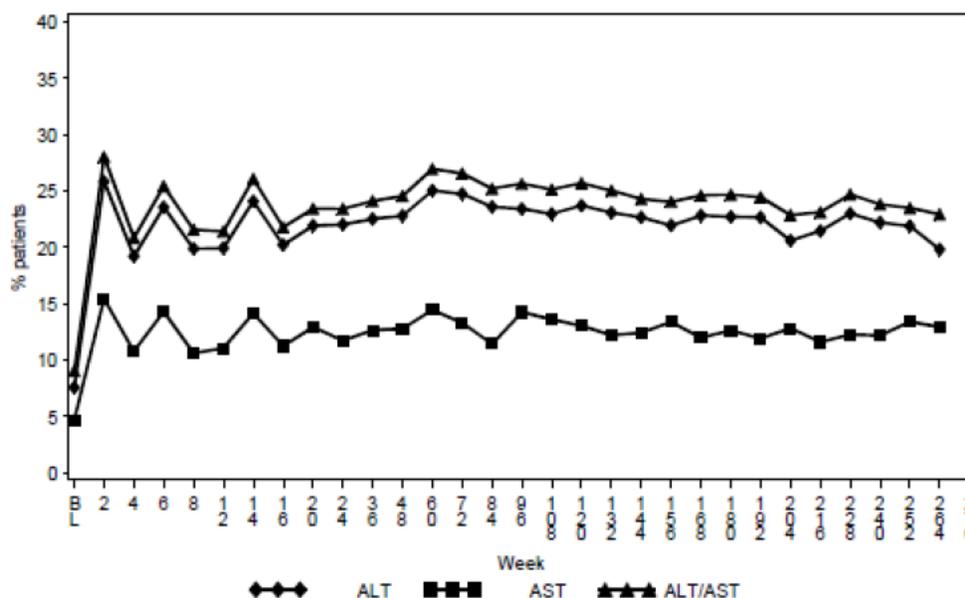
Table 10. ALT and AST Shifts from Normal at Baseline to Worst Post-Baseline Value During Long-Term Extension Studies

	Transaminase	All TCZ (n=4009)
Number of Patients with an increase from normal baseline to >ULN to 3 x ULN	ALT	2207/3696 (60%)
	AST	2127/3818 (56%)
Number of Patients with an increase from normal baseline to >3 to 5 x ULN	ALT	326/3696 (9%)
	AST	121/3818 (3%)
Number of Patients with an increase from normal baseline to >5 x ULN	ALT	107/3696 (3%)
	AST	31/3818 (1%)
Number of Patients Withdrawn from Study due to Transaminase Elevations		99/4009 (3%)

*Adapted from sponsor's Clinical Safety Summary: Table 49, page 153.

Importantly, there was no trend for an increased risk of transaminase level increasing over time, as the elevations remained stable over time (Figure 3). Increases of bilirubin from normal at baseline to ≥ULN were observed in 654/3995 (17%) of patients with 83% of patients demonstrating bilirubin levels in the high normal range, 16% >ULN to 3 x ULN, and <1% of patients with bilirubin levels >3 x ULN.

Figure 3. Rate of ALT and AST Elevations >ULN to 3 x ULN Over Time During the Long-Term Extension Studies



*Adapted from sponsor's Clinical Safety Summary: Figure 4, page 154..

The sponsor analyzed the laboratory data and found that eight patients met criteria for Hy's Law (defined as >3 x ULN transaminase elevation and concurrent >2 x ULN total bilirubin elevation). All eight patients had alternative explanations/etiologies for the elevated hepatic tests. Five of the patients have been previously discussed in previous submissions. Three new cases are contained in the current submission and their narratives are discussed briefly here:

- Patient 50914/6773 was a 42-year-old male randomized to the TCZ 8 mg/kg + MTX treatment arm and subsequently enrolled in the LTE study where he continued to receive active therapy. During this period the patient developed Hepatitis B and was subsequently withdrawn from the study.
- Patient 46723/2296 was a 59-year-old female with a past medical history significant for anticardiolipin antibodies (IgG) and tobacco use who was randomized to receive placebo + MTX. Following completion of the placebo-controlled study, she enrolled in the LTE study and received initial treatment with TCZ 4 mg/kg + MTX and then after Week 52, the dose was increased to TCZ 8 mg/kg + MTX. After approximately four years on TCZ therapy she developed elevations in her transaminases and bilirubin levels. Diagnostic investigation revealed portal vein and left hepatic vein thromboses that resulted into acute liver failure and death.
- Patient 60226/7679 was a 69-year-old female randomized to the placebo + MTX treatment arm and then subsequently received TCZ 8 mg/kg + MTX during the LTE study. Transaminase and bilirubin elevations were noted soon after initiation of TCZ + MTX and on Study Day 1513 met criteria for Hy's Law but was without clinical manifestations. Improvement following discontinuation of MTX was noted and she continued to receive TCZ and completed the study. This case was reported as a non-serious AE and did not lead to study discontinuation.

Postmarketing Global Safety Database and Epidemiologic Data

A total of 36 serious hepatic events in 31 patients were reported during the postmarketing experience resulting in an incidence rate of at least 0.06 events/100 PY (95% CI; 0.04, 0.08). The sponsor performed an unblinded medical review and found that 27 of the 31 patients had confounding factors (hepatotoxic drugs or underlying hepatic disease). Time to onset of the event ranged from 0 to 732 days after the first dose of TCZ. Ten of the cases appear to be transient increases in hepatic function tests without evident sequela and three cases were associated with malignancy. Two additional cases had the preferred term of ascites but the underlying etiology was not hepatic in origin. One of the 31 patients died as a result of their hepatic disease and two patients were withdrawn from the study.

A total of 105 hepatic enzyme abnormalities were reported as AEs in 92 patients resulting in a rate of at least 0.16 events/100 PY (95% CI; 0.13, 0.2). No further details were readily available.

Analyses using the MarketScan database showed a serious hepatic event rate in all RA patients as 0.09 events/100 PY and in RA patients treated with TNF antagonist as 0.07 events/100 PY. As per the sponsor's report, these data are consistent with what has been previously reported from other healthcare databases (PharMetrics and Protocare).

Elevations in hepatic transaminases and bilirubin are commonly known to occur in the RA patient population largely as a result of the hepatotoxic drugs (e.g., NSAIDs, MTX) commonly prescribed to treat the disease. Data is lacking to present an accurate incidence rate of transaminase and bilirubin elevations in the postmarketing settings.

In summary, the rate of serious hepatic events during the postmarketing experience (0.06 events/100 PY) was similar to the rate observed during the LTE studies (0.04 events/100 PY) and with the estimated rate of RA patients treated with TNF antagonists (0.07 events/100 PY). These data do not demonstrate an increased risk of TCZ-treated patients developing a serious hepatic event greater than what was already known from previously submitted data and is similar to what is observed in TNF antagonist-treated patients.

As a function of its mechanism of action, it is clear that TCZ treatment causes elevations in transaminases and bilirubin levels; however, taken in context with the rate of serious hepatic events, it is less clear whether TCZ-induced transaminase elevations result in increased serious hepatic events. During the postmarketing experience, four patients reporting a serious hepatic event also reported elevated transaminase levels but it is unclear that the elevations preceded the hepatic event. In fact, during the clinical trials the majority of patients with elevated transaminases had no clinical sequela. Review of the safety data also show that the frequency of elevated transaminases is greater when TCZ-treated patients receive concomitant therapy with DMARDs compared to TCZ monotherapy. In total, these data do not demonstrate an increased risk of serious hepatic events or increased elevation of liver enzymes over and above what was already known from analyses in previous submissions. Although serious hepatic events should continue to be monitored in the postmarketing setting, the current US package insert adequately addresses the known risks.

7.3.4.2 Gastrointestinal Perforations

Analyses of GI perforations were based on MedDRA preferred terms contained in the GI Perforation standard MedDRA queries. Since the events captured by the MedDRA terms are non-specific they may not correspond to actual GI perforations, consequently, the sponsor performed an unblinded medical review to the events using the following criteria to define a GI perforation:

- Description of perforation, or the term “perforation”, by the investigator in the SAE report or evidence perforation via imaging, surgery, or procedure
- All gross perforations were included regardless of confounding factors
- Microscopic abscesses and fistulas were not considered gross perforations

For the purposed of this submission, the rates for medically confirmed gross GI perforations are included for the clinical trials, while GI perforations that were identified with the MedDRA queries but not medically confirmed as GI perforations are listed for the LTE studies and postmarketing populations. The sponsor's unblinded adjudication of the cases of GI perforations is considered adequate and was previously agreed to with the Agency.

Placebo-Controlled Studies

During the placebo-controlled studies, all serious GI perforations were reported from patients who were receiving TCZ treatment and no serious GI perforations were reported in placebo-treated patients. A total of four GI perforations were reported in four DMARD-IR patients consisting of two events of diverticular perforation, one abdominal abscess, and one anal abscess. Given the sponsor's prior definition of GI perforations, the two cases of abscesses were excluded from the incidence rate of GI perforations resulting in an incidence rate of 0.2 events/100 PY (95% CI; 0.02, 0.60; Table 11). Two additional TCZ-treated patients reported a GI perforation, one patient from the MTX-naïve population, which resulted in death, and one patient from the TNF-IR population. All cases of GI perforation resulted in discontinuation of the patient from the relative study.

Table 11. Rate of Adjudicated GI Perforations/100 PY During the Placebo-Controlled Studies

	PBO + DMARD (n=1010)	TCZ+DMARD (n=1407)	TCZ+MTX (n=611)
DMARD-IR			
Number of Events	0	1	1
Exposure (PY)	543	841	427
Events/100 PY (95% CI)	-	0.1 (0, 0.7)	0.2 (0.01, 1.3)
MTX-Naive			
	PBO + MTX (n=190)	TCZ 8 mg/kg (n=193)	-
Number of Events	0	2	-
Exposure (PY)	92	96	-
Events/100 PY (95% CI)	-	1 (0.03, 5.8)	-
TNF-IR			
	PBO + MTX (n=160)	All TCZ (n=338)	-
Number of Events	0	1	-
Exposure (PY)	62	149	-
Events/100 PY (95% CI)	-	0.7 (0.02, 3.7)	-
Pooled Population			
	Placebo	TCZ	
Events/100 PY (95% CI)	1.5 (0.7, 2.7)	1.6 (1, 2.4)	

*Adapted from sponsor's Clinical Safety Summary: Table 52, page 160.

Long-Term Extension Studies

A total of 30 adjudicated GI perforation events in 29 patients were reported during the LTE studies resulting in a rate of 0.2 events/ 100 PY (95% CI; 0.1, 0.3). The rate of GI perforations was comparable across the different study populations. Twenty-nine of the 30 events have been reported in previous submissions. The new case reported in the current submission resulted from a diverticular perforation, and in fact, perforated diverticula accounted for 18 of the 30 events of GI perforations. When analyzed by 12-monthly periods, there was no increase in the rate of GI perforation events over time.

Twenty-seven of the 29 patients had one or more confounding factors including underlying medical conditions (e.g., diverticulitis) or concomitant drugs (e.g., corticosteroids), which are known to predispose to GI perforations. The sponsor constructed a proportional hazards model for the risk of developing a GI perforation based on patients with a history of diverticulitis, concomitant corticosteroid use, and age. The hazard for developing a GI perforation at any given time was calculated to be approximately four-fold higher in patients with a history of diverticulitis, approximately two-fold higher in patients with concomitant corticosteroid use, and approximately three-fold higher in patients 65 years of age or older.

Postmarketing Global Safety Database

A total of 149 GI perforation events in 120 patients were reported in the postmarketing population resulting in a rate of at least 0.23 events/100 PY (95% CI; 0.2, 0.3). The sponsor reanalyzed the postmarketing reports and concluded that some of the events were not consistent with the adjudicated definition of GI perforation. The adjudicated reports included 96 events in 94 patients with an estimated rate that was comparable, albeit lower, to the non-adjudicated reports, at 0.15 events/100 PY (95% CI; 0.1, 0.2). Six of the cases were fatal. As expected, the majority of the patients had confounding factors including concomitant medications and comorbidities. The time of onset ranged from 0 to 1251 days after the initial dose of TCZ.

The MarketScan database was used to estimate the background incidence rate of GI perforations in RA patients treated with TNF antagonists to be 0.18 events/100 PY (95% CI; 0.12, 0.22). This rate is comparable to rates reported in the literature for other healthcare databases in the same patient population^{8, 9}.

Overall, the reporting rates of GI perforations in the postmarketing setting was similar to the rate of GI perforations reported in the LTE population and the rates reported in the MarketScan database and literature for RA patients treated with TNF antagonists. Although the rate of GI perforations in the TCZ-treated patients appears to be similar to patients treated with TNF antagonists, there appears to be an increased rate compared to patients not treated with TCZ as evidenced by the data observed in the placebo-

8 Curtis JR et al. Arthritis Rheum. 2011 Feb;63(2):346-51

9 Curtis JR et al Pharmacoeconom Drug Saf 2011 Nov;20(11):1150-8

controlled studies. The risk of GI perforations is adequately addressed in the current US package insert.

7.3.4.3 Serious Cardiovascular Events

Analyses of the safety dataset in the original BLA submission demonstrated elevations in LDL cholesterol and triglycerides in TCZ-treated patients and raised concerns of a possible long-term increase in CV sequela, e.g., myocardial infarction and stroke. Consequently, serious CV events have been analyzed in each of the TCZ submissions to identify whether a CV safety signal exists. To that end, serious CV events are reviewed in this submission and will be divided into three major components:

- Serious MI captured using the Myocardial Infarction SMQ Narrow
- Serious stroke, which includes ischemic and hemorrhagic strokes using the Hemorrhagic Cerebrovascular Conditions SMQ Narrow and Roche AEGT for ischemic cerebrovascular conditions but excludes transient ischemic attacks (TIA)
- Cardiac death captured by review of death listings

Additionally, the sponsor analyzed hypertension using the MedDRA term Hypertension SMQ Narrow, and lipid laboratory abnormalities using the Roche standard AEGT for lipid lab abnormalities.

Placebo-Controlled Studies

A total of six MIs were reported during the placebo-controlled studies, five occurred in DMARD-IR patients and one was from the TNF-IR population. Of the five MIs involving DMARD-IRs, three were randomized to a TCZ treatment arm and two were randomized to receive placebo. One placebo-treated patient died and the remaining four patients had completely recovered. The calculated incidence rate for placebo-treated patients was 0.37 MI events/100 PY (95% CI; 0.04, 1.33) and 0.24 MI events/100 PY (95% CI; 0.05, 0.69) for TCZ-treated patients.

A total of eight strokes, excluding TIAs, were reported during the placebo-controlled studies. Seven of the strokes occurred in the DMARD-IR population of which six patients were randomized to a TCZ treatment arm. The remaining stroke event occurred in a patient from the TNF-IR population. The incidence rate of serious stroke in the DMARD-IR population was calculated at approximately 0.5 events/100 PY (95% CI; 0.2, 1). There was no apparent relationship to the type or cause of stroke among the eight cases. Two of the cases were found to be carotid artery occlusion with no neurologic deficits and thus misreported under the stroke MedDRA preferred term. Removal of these two events would be expected to lower the estimated incidence rate for TCZ-treated patients during the placebo-controlled study period (not calculated).

A total of four cardiac deaths were reported during the placebo-controlled studies, three in TCZ-treated patients and one patient randomized to the placebo treatment arm. The cardiac deaths have been submitted and reviewed in previous submissions.

In general, analysis of the safety dataset during the placebo-controlled studies failed to demonstrate a safety signal regarding an increase in Stage 1 or Stage 2 hypertension from baseline to the end of the placebo-controlled period in any of the study populations. Similarly, changes in lipid and triglyceride levels for the placebo-controlled studies have been reviewed in previous submissions and the findings do not vary when analyzed by patient population.

Long-Term Extension Studies

A total of 38 serious MI events were reported in 37 patients during the placebo-controlled studies resulting in an overall rate of approximately 0.3 serious MI events/100 PY (95%; 0.2, 0.4). Six of the events occurred within the first six-months of TCZ treatment but the overall rate remained stable over time. A total of 28 DMARD-IR patients experienced a serious MI for an overall incidence rate of approximately 0.3 events/100 PY (95% CI; 0.3, 0.4) compared to six TNFR-IR patients resulting in a rate of 0.4 events/100 PY (95% CI; 0.2, 0.9). The apparent increased rate of MI events in the TNF-IR population compared to the DMARD-IR population is likely not clinically significant given the overlapping CI and the relatively small number of patients experiencing an MI in the TNF-IR population. Thirty-one patients had at least one underlying risk factor for heart disease. Seven patients died as a result of an MI, four DMARD-IR patients and three TNF-IR patients.

A total of 37 serious stroke events were reported in 37 patients during the LTE studies resulting in an incidence rate of approximately 0.3 events/100 PY (95% CI; 0.2, 0.3). Twenty-seven (73%) of the 37 patients were over the age of sixty, a known risk factor for stroke. There were no differences in the rates of stroke between patient populations. The initial rate of strokes was highest during the first 12 months after starting treatment with TCZ but the rate remained stable afterwards. Five of the patients died as a result of their stroke.

Twenty cardiac deaths in 20 patients were reported during the LTE studies resulting in a rate of approximately 0.1 event/100 PY (95% CI 0.2, 0.2). The individual deaths have been discussed in previous submissions.

A total of 20 serious cases of hypertension in 18 patients were reported during the LTE studies for an overall rate of serious hypertension of approximately 0.1 event/100 PY (95% 0.1, 0.2). There were no differences in the rate of serious hypertension events among the different populations. The pattern of LDL and triglyceride levels remained stable during the LTE studies with no signs of further increases with continued TCZ treatment. The percentage of TCZ-treated patients with an LDL level \geq 130 mg/dL at baseline increased from 29% at baseline to approximately 50% from the first 6-months onward. In general, patients receiving lipid-lowering drugs are less likely to have an increase in lipid levels compared to patients not receiving lipid-lowering drugs. These analyses have been submitted in previous submissions.

Postmarketing Global Safety Database and Epidemiologic Data

There were 60 serious MI events in 59 patients reported during the postmarketing period leading to an estimated rate of at least 0.09 events/100 PY (95% CI: 0.07, 0.12). Fourteen of the MI events resulted in death and 38 of the 59 patients reported the MI within 6 months of initiating TCZ treatment. Rates of MI events were lower in Japan (0.06 events/100 PY) compared to the ROW region (0.11 events/100 PY) but the 95% CIs were overlapping.

A total of 96 serious stroke events in 87 patients were reported during the postmarketing experience with an estimated incidence rate of at least 0.15 events/100 PY (95% CI: 0.12, 0.18). Twenty-five of the 87 patients died from their stroke. The sponsor performed an additional search using a strategy which included TIA events resulting in 107 events in 97 patients. Fifty-one of these patients developed the stroke within 6 months of initiating TCZ. In fact, the overall time to event was within 12 months for approximately 60% of patients.

Forty-six cardiac deaths were reported in the postmarketing population with an estimated rate of at least 0.07 events/100 PY (95% CI: 0.05, 0.09). Among the cardiac deaths, there were 11 cases of cardiac arrest, 14 cases of MI, ten cases of heart failure, and four cases of cardiorespiratory arrest.

During the postmarketing period, the overall reporting rate for serious hypertension was estimated to be at least 0.07 events/100 PY (95% CI: 0.05, 0.09). Accurate assessment of abnormal lipid levels in the total postmarketing population was not quantifiable and is not likely to add additional useful information.

Epidemiological Studies/MarketScan Database

A search of the MarketScan database for CV events in RA patients treated with TNF antagonists was performed using definitions based on ICD-9 codes including hospitalized occurrences of MI, acute coronary syndrome, and cerebrovascular accident. The results of the search estimated the background rates of serious CV event in this patient population at approximately 0.6 MI events/100 PY (95% CI: 0.6, 0.7), 0.5 acute coronary syndrome events/100 PY (95% CI: 0.5, 0.6), and 0.7 cerebrovascular accident events/100 PY (95% CI: 0.6, 0.7). Literature reports of rates of MIs and strokes in the RA patient population ranged from 0.27 to 0.47 MI events/100 PY and 0.11 to 0.76 stroke events/100 PY (ref pp. 189). Hypertension is prevalent in the RA population and has been reported to range from 52% to 73% in most large community-based studies.

In summary, the estimated rate of serious MI, serious stroke, and cardiac deaths among TCZ-treated patients were not increased compared to the rates reported in clinical trials or those rates estimated for RA patients treated with TNF antagonists. In fact, the overall incidence rate for these three AEs was similar between TCZ-treated patients and placebo-treated patients. As discussed in previous reviews, the mean/median LDL and triglyceride levels increased with initiation of TCZ in all patient populations but remained stable with continued treatment. The data submitted to date do not support a link

between TCZ-induced increases and LDL and triglyceride concentrations and increases in CV events; however, this may be due in part from healthcare providers' pharmacologically managing the lipid elevations or insufficient longitudinal data given that the causative effect of lipid elevations and CV disease likely occurs over a long period of time. Data from the PMR will help to evaluate the risk of the long-term effects of TCZ treatment and serious CV disease.

7.3.4.4 Hypersensitivity and Anaphylaxis

Hypersensitivity and anaphylaxis have been reported with infusions of TCZ during clinical development and in the postmarketing setting regardless of dose, and with or without concomitant RA therapies, premedication, or previous hypersensitivity reaction. The events have been reported as early as the first infusion. Changes to the package insert and a "Dear Healthcare Professional" letter was sent by the sponsor on September 7, 2010 updating physicians of the occurrence of fatal cases of anaphylaxis in the postmarketing setting.

For the analyses presented in this submission, the sponsor used the following definitions to analyze the occurrence of hypersensitivity and anaphylaxis:

- Hypersensitivity events were all AEs that occurred ≤24 hours of an infusion and that were not judged as 'unrelated' to treatment by the investigator.
- Clinically significant hypersensitivity events were hypersensitivity events that led to patient withdrawal from treatment
- Serious hypersensitivity events were hypersensitivity events that were reported as an SAE
- Anaphylaxis events were events encompassed by the MedDRA preferred term Anaphylactic Reaction SMQ Narrow occurring within the first 24 hours of TCZ infusion
- Anaphylaxis events based on Sampson's criteria was used to further assess the occurrence of anaphylaxis related to treatment with TCZ to the clinical study database and postmarketing global safety database

Placebo-Controlled Clinical Studies

The majority of AEs reported as hypersensitivity events consisted of nausea, headache, dizziness, fatigue, hypertension, and transaminase elevations. Sixteen of 360 (4%) hypersensitivity events reported in the TCZ-treated DMARD-IR population led to withdrawal of treatment compared to one of 130 (<1%) events in placebo-treated DMARD-IR patients. The incidence rate of anaphylaxis in the DMARD-IR population was 0.24 events/100 PY (95% CI: 0.05, 0.69). Three of the events in TCZ-treated patients were deemed anaphylactic reactions, of which two were reported as an SAE. One patient was discontinued from treatment due to an SAE of syncope and another patient was discontinued due to a hemorrhagic stroke. In total, 9 of the 360 events in the TCZ-treated DMARD-IR population were reported as an SAE compared to none in the placebo treatment arm. No cases of hypersensitivity were reported as anaphylaxis in the MTX-naïve or TNF-IR

populations. No deaths occurred as a result of a hypersensitivity/anaphylactic reaction during the placebo-controlled studies.

Long-Term Extension Studies

The overall rate of hypersensitivity events was approximately 11 events/100 PY (95% CI: 10, 11) with the highest rate occurring during the initial 12 months (~26 events/100 PY) of TCZ treatment and decreasing significantly by month 36 (~5 events/100 PY). The majority of AEs did not lead to withdrawal of treatment and were not reported as an SAE.

A total of 9 cases of anaphylaxis occurred during the LTE studies resulting in a rate of ~ 0.06 events/100 PY (95% CI: 0.03, 0.11). All of the cases have been reported in previous submissions. Three of the cases occurred during the placebo-controlled period of the studies. Using Sampson's criteria, an additional two cases of anaphylaxis were identified in TCZ-treated patients; however, upon medical review, neither of the events was found to be anaphylaxis. One patient experienced upper abdominal pain and pruritic rash and was treatment was not discontinued. The second patient developed chest pain during the infusion but not withdrawn from treatment.

Postmarketing Global Safety Database

During the postmarketing setting, an estimated reporting rate for serious hypersensitivity events was at least 0.16 events/100 PY (95% CI: 0.13, 0.2). During this period, 67 anaphylaxis events in 65 patients were reported resulting in an incidence rate of at least 0.1 anaphylactic events/100 PY (95% CI: 0.08, 0.13). On review of the cases, 58 of the events were deemed consistent with anaphylaxis. Five cases reported as anaphylaxis resulted in death; however, after medical review only two of the cases met the definition of anaphylaxis.

Overall, the rate of anaphylaxis in the postmarketing period was comparable with the rate observed in the LTE extension study and approximately half of the rate observed during the placebo-controlled period. Given the seriousness and unpredictability of TCZ-associated anaphylaxis the Agency sent an information request to the sponsor to assess whether a minimum duration of time for monitoring for these events could be incorporated into the US package insert.

The sponsor's analysis looked at all data regarding cases of potential anaphylaxis through October 10, 2012 (cutoff for the 4-month safety update). After medical review, a total of 65 cases were considered anaphylaxis with 48 of the cases occurring during TCZ infusion and three events occurring after infusion. Of the three cases occurring after infusion, one occurred 4 hours after infusion, one case occurred the same day (unknown timing), and the third case occurred one hour after infusion but it is unclear whether the one-hour time period relates to post-infusion or from the start of infusion. The onset of anaphylaxis for 14 cases is unknown. Two of the reported cases resulted in death with anaphylaxis onset occurring during TCZ infusion. The sponsor concluded, and the Agency agrees, that given the evidence

that the majority of cases of anaphylaxis, including the two deaths, occurred during TCZ infusion, that it would be difficult to identify a specific time period post-infusion that would increase capture of anaphylaxis/hypersensitivity event and that additional language to the US package insert is not warranted at the present time.

7.3.4.5 Serious Infections

The RA population in general is at a higher risk for serious infections due to their underlying disease and immunosuppressive drugs used to treat the disease. Given the underlying mechanism of TCZ and its potential for immunosuppression the rate and types of serious infections were assessed.

Overview of Serious Infections

Placebo-Controlled Studies

Overall, TCZ-treated patients demonstrated a higher rate of serious infections compared to placebo-treated patients during the placebo-controlled studies (Table 12). The rate of serious infections was essentially similar among all subpopulations of patients treated with TCZ (data not shown). The most common types of serious infections in TCZ-treated patients were pneumonia and cellulitis. Of the nine DMARD-IR patients reported to have cellulitis, all were from the TCZ 8 mg/kg treatment arm.

Table 12. Rates of Serious Infections (Pooled Patient Population)

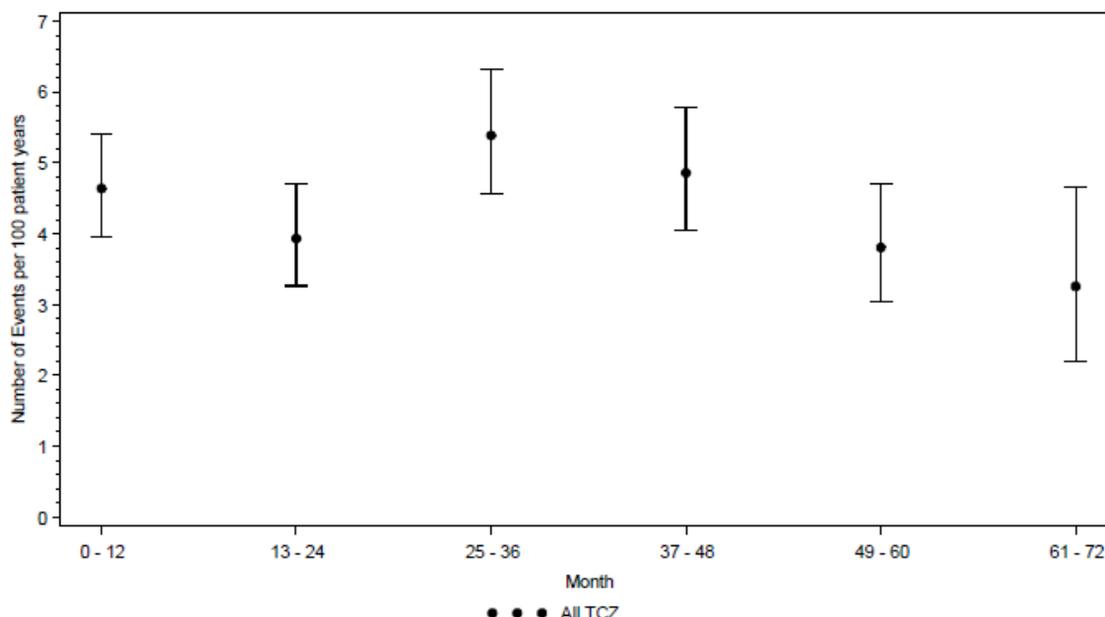
Placebo-Controlled Studies in DMARD-IR Patients				
	Placebo	All TCZ	LTE Studies	Postmarketing Data
TCZ Exposure (PY)	543	1268	14994	65099
Serious Infections				
Number of events	17	58	668	1507
Events/100 PY	3.13	4.57	4.46	2.31
95% CI	1.83, 5.02	3.47, 5.91	4.12, 4.81	2.20, 2.43
Serious Opportunistic Infections				
Number of events	0	2	10	58
Events/100 PY	NC	NC	0.07	0.09
95% CI	-	-	0.03, 0.12	0.07, 0.12
Tuberculosis				
Number of events	0	0	16	24
Events/100 PY			0.11	0.04
95% CI			0.06, 0.17	0.02, 0.05
Serious Pneumonia				
Number of events	4	14	142	361
Events/100 PY	0.74	1.1	0.95	0.55
95% CI	0.2, 1.89	0.60, 1.85	0.80, 1.12	0.50, 0.61
Fatal Infections				
Number of events	1	4	25	89
Events/100 PY	NC	NC	0.17	0.14
95% CI			0.11, 0.25	0.11, 0.17

*Adapted from sponsor's Clinical Safety Summary: Table 75, page 202.

Long-Term Studies

The overall incidence rate of serious infections in TCZ-treated patients was approximately 4.5 events/100 PY (95% CI: 4.1, 4.8) during the LTE studies (Table 12) and there was no increase in the rate of infections over time (Figure 4). The most common serious infections during the LTE studies were pneumonia (0.73 events/100 PY) and cellulitis (0.52 events/100 PY). Other serious infections with rates ≥ 0.1 events/100 PY but ≤ 1.2 events/100 PY were urinary tract infections, diverticulitis, gastroenteritis, bronchitis, and erysipelas. These data have been reviewed in previous submissions.

Figure 4. Rate of Serious Infections/100PY by 12-Month Periods During the Long-Term Extension Studies.



*Adapted from sponsor's Clinical Safety Summary: Figure 8, page 205.

Postmarketing Global Safety Database

A total of 1507 serious infections were reported in 1227 patients resulting in an incidence rate of at least 2.31 events/100 PY (95% CI: 2.2, 2.43; Table 12). The most common serious infections were pneumonia (0.29 events/100 PY), cellulitis (0.2 events/100 PY), sepsis (0.1 events/100 PY), herpes zoster (0.1 events/100 PY), and septic shock (0.05 events/100 PY).

Epidemiological Studies

Published rates of serious infections in the RA population range from 3.4 events/100 PY^{10,11} to 10.1 events/100 PY. Data from Galloway et al¹¹ reported an incidence rate of 4.2 events/100 PY (95% CI: 3.97, 4.38) from approximately 12,000 RA patients treated with TNF antagonists with greater than 36,000 PY of longitudinal data.

Thus, the estimated overall rate of serious infections (including opportunistic and TB infections) is comparable to the rate observed in the placebo-controlled and LTE studies as well as reports in the literature regarding incidence rates of serious infections for patients treated with TNF antagonists.

Deaths from Infections

Placebo-Controlled Studies

Five patients died as a result of infection during the placebo-controlled studies. All five patients were from the DMARD-IR population with four patients randomized to

10 Favalli EG et al. Autoimmun Rev. 2009 Jan;8(3):266-73

11 Galloway JB et al. Ann Rheum Dis. 2011 Oct;70(10):1810-4

TCZ treatment arm and one patient to placebo. Of the four TCZ-treated patients, two died of sepsis, one died of bronchopneumonia, and one died of gastrointestinal infection. The single placebo-treated patient died from pneumonia.

Long-Term Extension Studies

A total of 25 patients from the LTE population died resulting in a rate of 0.17 deaths from infection/100 PY (95% CI: 0.11, 0.25). The rate of death from infections did not increase over time. Four new deaths from infections are reported since the last TCZ submission and were all due to pneumonia. Of the total 25 deaths from infections, 10 were from pneumonia, 10 from sepsis, two from endocarditis, one from gastrointestinal infection, one from CNS infection, and one from bronchitis.

Postmarketing Global Safety Database

There were 89 deaths from infection in the postmarketing experience resulting in an incidence rate of at least 0.14 events/100 PY (95% CI: 0.11, 0.17). The most common fatal infections were pneumonia and sepsis. Of the 89 patients who died, 39 were 70 years of age or older.

Epidemiological Studies

A study comparing rates of cause-specific mortality in two RA patient cohorts reported a death rate due to infection as 0.24 events/100 PY for biologic-treated patients and 0.58 events/100 PY for patients not receiving biologic therapies¹².

Overall, the rate of death due to infections during the TCZ postmarketing experience is comparable to the rate of death observed during the TCZ clinical trials and with the death rate due to infections observed in patients treated with TNF antagonists.

Pneumonia

Placebo-Controlled Studies

Pneumonia was the most frequently reported serious infection in the DMARD-IR, MTX-naïve, and TNF-IR populations. In DMARD-IR patients, a total of 14 cases of serious pneumonia were reported in TCZ-treated patients (1.1 events/100 PY; 95% CI: 0.6, 1.85) compared to 4 cases reported in placebo-treated patients (0.74 events/100 PY; 95% CI: 0.2, 1.89). In total, 26 patients reported cases of serious pneumonia during the placebo-controlled studies. Seven of the patients were withdrawn from treatment. Two of these patients died, both of who were DMARD-IR population, one received TCZ treatment and the other was randomized to receive placebo.

Long-Term Extension Studies

A total of 142 cases of serious pneumonia were reported in 128 patients during the LTE studies resulting in a rate of 0.95 events/100 PY (95% CI: 0.80, 1.12). This rate remained stable over time. Pneumonia was the most common type of infection responsible for a fatal outcome accounting for ten patient deaths.

12 Carmona et al. Ann Rheum Dis. 2007 Jul'66(7):880-5

Postmarketing Global Safety Database

A total of 361 cases of serious pneumonia were reported in 340 patients during the postmarketing experience resulting in an estimated rate of at least 0.55 events/100 PY (95% CI: 0.5, 0.61).

Epimemiological Studies

Published data from the literature estimated the incidence rate of pneumonias requiring hospitalization as 0.84 events/100 PY in RA patients identified from the PharMetrics claims database¹³.

Overall, the rate of serious pneumonias in TCZ-treated patients is greater than placebo-treated patients but is comparable to the rate observed in TCZ-treated patients during the clinical trials as well as the rates of pneumonia described in patients with RA treated with TNF antagonists.

Opportunistic Infections

Placebo-Controlled Studies

Two cases of opportunistic infections were reported during the placebo-controlled studies: one case of pneumocystis jirovecii pneumonia, and one case of candida osteomyelitis. These cases have been reviewed in previous submissions.

Long-Term Extension Studies

A total of ten opportunistic infections were reported in ten patients of the LTE population for an overall rate of 0.07 events/100 PY (95% CI: 0.03, 0.12). The ten infections included two cases of systemic candida, two cases of fungal sinusitis, and one case each of coccidioidomycosis, candida osteomyelitis, pneumocystis jirovecii pneumonia, cryptococcal pneumonia, m. avium complex infection, and alcaligenes infection. The two systemic candida infections resulted in death.

Postmarketing Global Safety Database

Of the total 58 reports of serious opportunistic infections, 43 events were reported from Japan. The rate of serious opportunistic infections from Japan was 0.17 events/100 PY compared to 0.04 events/100 PY in ROW countries. The differences in rates of opportunistic infections most likely stems from the higher reporting rate of pneumocystis jirovecii pneumonia in Japan (25 cases) vs. ROW countries (3 cases).

Epidemiology

Smitten et al¹³ reported an incidence rate of 0.07 opportunistic infections requiring hospitalization/100 PY using the PharMetrics claims database for RA patients. Specific drugs used to treat the patients were not identified and likely included DMARDs as well as biologic therapeutic drugs.

Excluding the postmarketing data from Japan, the overall rate of opportunistic infections during the postmarketing experience was similar between TCZ-treated patients and that

13 Smitten AL et al. J Rheumatol 2008 Mar;35(3):387-93

observed in the clinical trials and the incidence rate reported in TNF antagonist-treated patients with RA.

Tuberculosis

Placebo-Controlled Studies

There were no cases of TB reported during the placebo-controlled studies.

Long-Term Extension Studies

A total of 16 cases of TB in 14 patients were reported in the LTE population for an incidence rate of 0.11 events/100 PY (95% CI: 0.06, 0.17). Five of the cases of TB are being reported in this submission for the first time. There was a numerically higher number of TB cases after 24 months of TCZ treatment compared to the first 24 months of treatment. The clinical significance is difficult to ascertain given the small number of events and overlapping 95% CIs. The sponsor's medical review suggested that 13 of the patients had de novo TB and 1 patient had reactivation of latent TB. None of the TB cases were fatal.

Postmarketing Global Safety Database

A total of 24 cases of TB in 24 patients were reported during the postmarketing experience for a rate of 0.04 events/100 PY (95% CI: 0.02,0.05). This rate is lower and consistent with the rate observed during the LTE studies. There were no differences between regions or subpopulation.

Epidemiology

A recent report in the literature reported the rate of TB in RA patients treated with TNF antagonists was approximately 0.1 event/100 PY (0.06, 0.14)¹⁴. Other studies report TB infection rates in the RA population ranging from 0.02 events/100 PY to 0.12 events/100 PY.

Overall, the rate of TB infections during the postmarketing experience was similar between TCZ-treated patients and that observed in the LTE studies and the incidence rate reported in TNF antagonist-treated patients with RA.

Neutropenia

A reduction in circulating neutrophil counts has been reported with TCZ treatment believed to be mediated by the TCZ-induced anti-IL6 antagonism. Consequently, events of neutropenia were analyzed.

Placebo-Controlled Studies

At baseline, greater than 98% of patients had neutrophil counts within normal range at baseline in all patient populations. By week 2, only approximately 85% to 90% of TCZ-treated patients had normal neutrophil counts with subsequent levels remaining stable with further TCZ treatment. In all patient populations, the majority of patients with

¹⁴ Dixon et al Ann Rheum Dis. 2012 Mar;69(3):522-8

reported lower than normal neutrophil counts had Grade 1, and to a far lesser degree Grade 2, neutropenia. A total of 58 out of 1991 (3%) DMARD-IR patients had Grade 3 or 4 neutropenia during the randomized control studies compared to 4% and 3% of MTX-naïve and TNF-IR populations, respectively. No patient reported a serious infection during the randomized control studies.

Long-Term Extension Studies

A total of 2163 out of 4002 (54%) patients in the LTE studies maintained a normal neutrophil count for the duration of treatment. Of the remainder of patient who did not maintain a normal neutrophil count during the LTE studies, 871 (22%) patients had a Grade 1 neutropenia, 723 (18%) patients had Grade 2 neutropenia, 212 (5%) patients had Grade 3 neutropenia, and 33 (<1%) had Grade 4 neutropenia. Grade 3 neutropenia was not sustained for the majority of the 245 patients and neutropenia on three or more consecutive visits was reported for 19 (8%) patients. Only one patient with Grade 3/4 neutropenia experienced a serious infection.

Postmarketing Global Safety Database

A total of 100 events of neutropenia in 90 patients were reported in the postmarketing population giving an estimated incidence rate of approximately 0.15 events/100 PY (95% CI: 0.12, 0.19). Forty-five events were spontaneous reports and 55 events occurred during the clinical studies. The degree of neutropenia was not feasible to ascertain in the postmarketing experience as a result of missing data. Of the 90 patients reporting neutropenia, 13 patients also reported a serious infection(s) within 30 days around the time of the neutropenia report. Two of these patients died from the infection. A reliable estimate of neutropenia in RA patients, in general or those treated with TNF antagonists, for comparison was not available in the published literature or other epidemiologic source.

Overall, there did not appear to be an overt risk of serious bleeding or thrombocytopenia that would alter the risk-benefit profile of TCZ for the treatment of patients with moderately to severely active RA.

7.3.4.6 Serious Bleeding Events and Thrombocytopenia

Serious bleeding events were evaluated as a result of thrombocytopenia being observed in the TCZ development program. To evaluate events the sponsor used the following MedDRA preferred terms:

- Serious bleeding event: to assess rates of serious bleeding the sponsor used the MedDRA preferred term contained in Hemorrhage Term SMQ Wide
- Thrombocytopenia: for the postmarketing experience only, the rate of thrombocytopenia was assessed using the preferred term Hematopoietic Thrombocytopenia SMQ Wide

Placebo-Controlled Clinical Studies

A total of nine patients reported a serious bleeding event during the placebo-controlled studies, five TCZ-treated patients (two hemorrhagic strokes, rectal hemorrhage, Mallory-Weiss Syndrome, uterine hemorrhage) and four placebo-controlled patients (GI

hemorrhage, hemoptysis, subarachnoid hemorrhage, metrorrhagia). None of the serious bleeding events were associated with thrombocytopenia.

Long-Term Extension Studies

A total of 65 serious bleeding events in 59 patients were reported in the LTE population resulting in an incidence rate of 0.43 events/100 PY (95% CI: 0.33, 0.55). The most frequent types of bleeding events were related to the GI tract, which may reflect the RA populations' predisposition to GI bleeding given their concomitant use of NSAIDs and corticosteroids. The rate and types of events did on change over time. Six out of seven patients who died from serious bleeding events had normal platelet counts, while one patient had a platelet count of $96 \times 10^9/L$, which should not have increased the patient's risk of a bleeding event.

Postmarketing Global Safety Database and Epidemiologic Data

A total of 187 serious bleeding events in 169 patients were reported in the postmarketing experience for a rate of 0.29 events/100 PY (95% CI: 0.25, 0.33). The most frequently reported serious bleeding event was 28 cases of disseminated intravascular coagulation disorder (0.04 events/100 PY) with 22 of the cases being associated with sepsis or infection. The other six cases were TTP, renal failure with pulmonary alveolar hemorrhage, histiocytosis hematophagocytosis, thrombocytopenia, and acute pancreatitis, infective arteritis. A reliable estimate of serious bleeding events in RA patients, in general or those treated with TNF antagonists, for comparison was not available in the published literature or other epidemiologic source.

Thrombocytopenia

Placebo-Controlled Studies

At baseline, all three of the patient populations had platelet counts that were near the ULN; however, following the first infusion of TCZ, mean and median platelet counts decreased but remained within the normal range. Mean platelet counts remained stable through the remainder of the treatment period. During the placebo-controlled studies, $\geq 99\%$ of patients had a normal platelet count at baseline and $\geq 95\%$ TCZ-treated patients maintained a normal platelet during treatment. Most of the patients that developed lower than normal platelet concentrations developed Grade 1 thrombocytopenia. Five patients from the DMARD-IR population were the only patients to report a Grade 3 or 4 thrombocytopenia: four TCZ-treated patients and one placebo-treated patient. None of the patients experiencing thrombocytopenia had a serious bleeding event.

Long-Term Extension Studies

Similar to the situation described in the placebo-controlled studies, the majority of patients in the LTE population demonstrated platelet counts near the ULN at baseline but experienced decreases toward normal and lower limits of normal following the initial TCZ infusion. A normal platelet count was maintained by approximately 81% (3245/4002) of patients for the duration of treatment with platelet counts remaining stable thereafter. Of the 19% of patients reporting thrombocytopenia, 16% reported Grade 1, 1.3% Grade 2, 0.4% Grade 3, and 0.3% Grade 4. Only three of the 32

patients reporting Grade 3 or 4 thrombocytopenia experienced a serious bleeding event; one case of DIC, one upper GI hemorrhage, and one stomatitis hemorrhage. In any 12-month period, approximately 90% of patients had normal platelet counts and 9% had Grade 1 thrombocytopenia. Less than 1% of patients at any given time had Grade 2, 3, or 4 thrombocytopenia. Additionally, platelet counts tended to remain stable over time and no individual patient had decreasing platelet counts over time.

Postmarketing Global Safety Database and Epidemiologic Data

The overall incidence rate for serious thrombocytopenia events in the postmarketing population was estimated to be at least 0.07 events/100 PY (95% CI: 0.05, 0.10). Three of the 47 patients with thrombocytopenia reported a serious bleeding event: two cases of DIC and one case of purpura. Given the nature of postmarketing safety reports, details regarding platelet level not reporting a serious bleed is unknown and makes drawing firm conclusions from the postmarketing population difficult. A reliable estimate of thrombocytopenia in RA patients, in general or those treated with TNF antagonists, for comparison was not available in the published literature or other epidemiologic source.

Overall, there did not appear to be an overt risk of serious bleeding or thrombocytopenia that would alter the risk-benefit profile of TCZ for the treatment of patients with moderately to severely active RA.

7.3.4.7 Demyelination Events

The Agency requested the sponsor to assess cases of demyelination in association with TCZ treatment and TNF antagonists. Analyses of serious demyelination events were based on preferred terms contained in the Demyelination SMQ Narrow term.

Placebo-Controlled Studies

No cases of serious demyelination events were reported during the placebo-controlled studies.

Long-Term Studies

Three serious demyelination events were reported in the LTE population: On case each of optic neuritis, demyelination encephalopathy, and multiple sclerosis relapse. The incidence rate was calculated to be 0.02 events/100 PY (95% CI: 0, 0.06).

Postmarketing Global Safety Database and Epidemiologic Data

A total of seven cases of serious demyelinating events were reported in the postmarketing population with an estimated rate of at least 0.01 events/100 PY (95% CI: 0, 0.02). The seven cases included two cases of multiple sclerosis, two cases of optic neuritis, and one case each of leukoencephalopathy, demyelination, and demyelinating polyneuropathy. There are no established rates of demyelination disorders in RA patients to compare to rates in the TCZ studies. Demyelinating events (e.g., multiple sclerosis, optic neuritis) have been reported in trials of TNF antagonists in the RA population.

Overall, there did not appear to be an overt risk of demyelination events that would alter the risk-benefit profile of TCZ for the treatment of patients with moderately to severely active RA.

7.3.5 Submission of Specific Safety Concerns

In addition to assessing the safety signals that lead to the restricted use of TCZ to TNF-IR RA patients, the Agency requested the sponsor also analyze AEs associated with serious pancreatitis, pancytopenia, convulsions, and interstitial lung disease.

7.3.5.1 Pancreatitis

Placebo-Controlled Studies

A single case of serious pancreatitis was reported in the placebo-controlled studies. Patient 50870/6813 had a past medical history significant for pancreatitis, diabetes, myositis, and RA that was inadequately treated with DMARD therapy (i.e., DMARD-IR). The patient was randomized to the TCZ 8 mg/kg + MTX treatment arm and on Study Day 14 experienced an event of pancreatitis. TCZ treatment was discontinued and supportive therapy was initiated resulting in resolution of the pancreatitis on Study Day 26 with no reported sequela.

Long-Term Extension Studies

A total of 16 events, in 13 patients, of serious pancreatitis were reported during the LTE studies with an approximate rate of serious pancreatitis of 0.1 event/100 PY (95% CI; 0.1, 0.2). Potential risk factors including comorbidities (e.g., cholelithiasis) and/or concomitant drugs (e.g., corticosteroids) were identified in 12 of the 13 patients at the time of the event. Patient 46752/1990 was receiving TCZ 8 mg/kg + MTX and developed serious pancreatitis on Study Day 1296 and died on Study Day 1299 due to cardiorespiratory arrest. Autopsy recorded the cause of death as pulmonary edema secondary to necrohemorrhagic pancreatitis. Patient 59407/85717, who had a significant past medical history of cholelithiasis, reported three separate events of pancreatitis on Study Days 141, 309, and 463 subsequently withdrew from the study.

There was no clear temporal association between the initiation of TCZ treatment as the onset of cases of serious pancreatitis ranged from 14 to 1890 days after starting therapy with 9 of the 16 cases starting after 1000 of TCZ treatment.

Postmarketing Global Safety Database and Epidemiologic Data

A total of 28 events in 25 patients were reported during the postmarketing period resulting in an estimated incidence of serious pancreatitis of 0.04 events/100 PY (95% CI; 0.03, 0.06). Of the 25 patients reporting events, 15 were from postmarketing studies and 10 patients were from spontaneous reports. Three of the patients died as a result of the pancreatitis.

Cannon et al¹⁵ estimated the incidence rate of pancreatitis in RA patients as 0.3 events/100 PY (95% CI; 0.2, 0.3) based on a retrospective study of insurance claims in the US in RA patients receiving non-biologic DMARDs.

In summary, the overall incidence rates of serious pancreatitis in TCZ-treated patients were lower than the reported incidence rates for RA patients in general. Although there did not appear to be a temporal relationship between the administration of TCZ and the onset of pancreatitis, listing of pancreatitis should be included in the package insert given the potential seriousness of the event.

7.3.5.2 Pancytopenia

For the purposes of this review, analyses of pancytopenia are based on events falling under the MedDRA preferred terms of pancytopenia, bone marrow failure, and in the placebo-controlled and LTE studies, laboratory criteria defined by Council for International Organization of Medical Science (CIOMS): hemoglobin <10 g/dL, neutrophils <1.5 x 10⁹/L, and platelets <100 x 10⁹/L.. Neutropenia is reviewed in Section 7.3.4.5 and thrombocytopenia is reviewed in Section 7.3.4.6.

Placebo-controlled Studies

No cases of pancytopenia were reported as an AE during the placebo-controlled studies; however, two placebo-treated patients were identified who met the CIOMIS defined criteria for pancytopenia.

Long-Term Extension Studies

A total of eight cases, in seven patients, of pancytopenia were reported as AEs during the LTE studies resulting in an overall incidence rate of 0.05 events/100 PY (95%CI; 0.02, 0.1). Of the eight cases, three were reported as SAEs of which one was fatal. The remaining five cases were reported as non-serious. Interestingly, six of the cases where neutrophils were recorded would not have met the CIOMIS definition for pancytopenia.

Analysis of patients' laboratory data during the LTE period identified an additional eight cases of pancytopenia in seven patients, based on the CIOMIS definition. None of these cases were reported as an AE and were not associated with infection. Adding these eight cases with the eight-reported AE did not alter the incidence of pancytopenia, which remained at 0.05 events/100 PY.

Postmarketing Global Safety Database and Epidemiologic Data

A total of 24 events of pancytopenia were reported in 22 patients during the postmarketing experience through April 1, 2011 resulting in an estimated incidence rate of 0.04 events/100 PY (95% CI; 0.02, 0.05). All events except for one were reported as SAEs. Twelve of the 22 cases were spontaneous reports, two were from the literature, six were from drug surveillance studies, one from a compassionate use study, and one was from an unknown trial. Eighteen of the patients reported pancytopenia, while four

15 Cannon et al. J Rheumatol. 2004 Oct; 31(10):1906-11

patients reported bone marrow failure. Two of the patients reporting bone marrow failure were undergoing concomitant chemotherapy treatment for hematologic malignancies, one patient was diagnosed with macrophage activation syndrome, and the fourth patient had no apparent underlying medical illness or potentially causative agent except for MTX.

Data for duration of TCZ exposure prior to the onset of the event was reported in thirteen patients and ranged from 22 days to 1461 days. This data does not provide a clear temporal relationship between TCZ and the onset of pancytopenia.

Pancytopenia has long been known to occur in patients with RA as well as with use of MTX. Lim et al¹⁶ reported an incidence rate of 1.9 events/100 PY in RA patients treated with MTX between 1999 and 2004. Incidence rates for RA patients treated with the TNF antagonists infliximab and etanercept have been estimated to be approximately 0.1 events/100 PY. Overall, the incidence rate of TCZ-associated pancytopenia was similar to the rate reported for patients in the general RA population receiving treatment with MTX and/or TNF antagonists.

7.3.5.3 Convulsions

Rates of convulsions are based on MedDRA preferred terms contained under the Convulsions narrow heading.

Placebo-Controlled Studies

Three, 'non-serious' cases of convulsions were reported as AE during the placebo-controlled studies, none of which were classified as a SAE or led to withdrawal from the study. Two of the convulsions occurred in the TCZ 8 mg/kg treatment arm of DMARD-IR patients and one case occurred in a placebo-controlled patient who was a DMARD-IR.

Long-Term Extension Clinical Studies

A total of 16 cases, in 12 patients, of convulsions were reported during the LTE studies resulting in an incidence rate of 0.1 events/100 PY (95% CI; 0.06, 0.17). While three of the events were classified as a SAE, none of the cases were fatal.

The 16 cases of convulsions occurred between Study Days 41 and 1016 with no consistent pattern observed in terms of a temporal relationship or type of seizure. The rate of convulsions was highest during the first 24 months but the overall number of events was small.

Postmarketing Global Safety Database

A total of 23 events, from 23 patients, were reported during the postmarketing experience with an estimated incidence rate of at least 0.04 events/100 PY (95% CI; 0.02, 0.05). Twenty-two of the 23 events were reported as a SAE. While 16 of the 23 patients did not have predisposing factors for a convulsion, seven of the patients had a

16 Lim et al. Rheumatology. 2005 Aug;44(8):1051-5

past medical history that may have predisposed to convulsions including three patients with a history of epilepsy, and four patients with confounding factors including concomitant drugs or convulsions reported with an infusion/procedure.

The incidence of seizures in the general population was estimated to range from 0.01 events/100 PY to as high as 0.4 events/100 PY. An increased risk of seizures has not been reported in patients with RA and data regarding the incidence of seizures in patients treated with TNF antagonist are lacking but a crude estimate based on reporting from the AERS database is approximately 0.02-0.03 events/100 PY.

Overall the rates of convulsions of patients treated with TCZ are similar to the rates reported in the AERS database for the TNF antagonist population and with the rates of the general US population. Additionally, no clear temporal relationship can be identified.

7.3.5.4 Interstitial Lung Disease

Analyses for cases of interstitial lung disease (ILD) were based on MedDRA preferred terms contained in the ILD wide classification. The broadened term was used to better capture the diagnosis of ILD given its variability in terms of disease classification and the limited tools available to diagnose the disease. New onset and exacerbation of ILD was captured for the clinical trial studies, while overall rates (i.e., new onset and exacerbation) were analyzed as one entity for the clinical trial and postmarketing datasets. Exacerbation of ILD was assessed by identifying whether patients had a history of ILD prior to baseline and had an ILD event while receiving TCZ and by reviewing the terms of all reported events where worsening, progression, or exacerbation is described regardless as to whether the patient had a previous diagnosis of ILD.

Placebo-Controlled Studies

A total of five ILD events were reported in TCZ-treated patients during the placebo-controlled studies with a calculated incident rate of 0.3 events/100 PY (95% CI; 0.1, 0.8). In comparison two placebo-controlled patients reported ILD events with a similar incidence rate of 0.3 events/100 PY (95% CI; 0.03, 1). Four of the TCZ-treated patients and one of the placebo-treated patients were from the DMARD-IR population and were reported as SAEs. The two patients who were not DMARD-IRs were diagnoses with sarcoidosis and rheumatoid lung but neither was reported as an SAE. The time of onset of ILD event varied between Study Day 16 to 225 with six of the seven events reported within the first 90 days of the study. All patients except for one had received previous MTX.

Long-Term Extension Studies

A total of 88 ILD events, in 80 patients, were reported in the LTE studies with an overall incidence rate of 0.6 events/100 PY (95% CI' 0.5, 0.7). Twenty-two of the events were reported as an SAE. Seven of the 80 patients reporting events had a past medical history significant for ILD. While the remaining 73 patients did not have a reported

medical history of ILD, review of the individual cases revealed that the specific diagnoses given to 9 patients suggested a pre-existing ILD diagnosis, e.g., “progression of ILD” or “worsening of pre-existing ILD”. Two deaths were reported due to ILD events and an additional two deaths suggested that ILD was a potentially contributing factor. All four deaths occurred in patients with no medical history of ILD.

A total of 65 of the 80 patients reported use of medications with known pulmonary toxicity, specifically, 62 patients had received MTX and 21 patients received leflunomide. Time to onset of ILD ranged from Study Day 1 to 1628 with 63% of patients reporting an event in the first 24 months of TCZ treatment.

Postmarketing Global Safety Database

A total of 102 events, in 100 patients, were reported as AEs during the postmarketing period with 97 reports being reported as SAEs. The estimated rate of ILD events during this period was at least 0.2 events/100 PY (95% CI; 0.1, 0.2). Of the 100 patients reporting an event, 44 had a previous medical history of ILD, pulmonary fibrosis, pulmonary sarcoidosis, or organizing pneumonia. Twenty-one of the 100 patients reporting an event died. Of these patients, 16 had a reported medical history significant for ILD.

Analysis by region demonstrated that 80 of the patients were from Japan resulting in a higher estimated incidence rate compared to the ROW, 0.3 events/100 PY (95% CI; 0.3, 0.4) vs. 0.05 events/100 PY (95% CI; 0.03, 0.08), respectively. The disparity in regions is believed to result from the greater awareness of the disease and more sensitive diagnostic methods in Japan. There was no clear temporal relationship between initiation of TCZ and the onset of the ILD event in the postmarketing dataset.

The annual incidence rate of ILD in the general US population is estimated at approximately 0.03 events/100 PY¹⁷. In contrast, published reports of ILD in the RA population ranges from 0.1 to 0.4 events/100 PY^{18,19,20}. The six-month incident rate in Japanese patients treated with TNF antagonist therapies has been reported to be approximately 1 event/100 PY²¹, while in the US the rate of ILD in RA patients using biologic disease modifying agents has been estimated to be approximately 0.1 event/100 PY²².

Overall, the incidence rate of ILD events ranged from 0.3-0.6 events/100 PY in TCZ-treated patients, which are comparable to the event rates observed in the general RA population. While the rate of events in the postmarketing experience (~0.6 events/100 PY) is higher than that seen in other studies, the placebo-controlled studies had

17 Coultas DB et al. *Am J Respir Crit Care Med*. 1994 Oct;150(4):967-72

18 Bongartz T et al. *Arthritis Rheum*. 2010 Jun;62(2):1583-91

19 Wolfe F et al. *Scand J Rheumatol* 2007 May-Jun;36(3):172-8

20 Koduri et al. *Rheumatology* 2010 Aug;49(8):1483-90

21 Nagai et al. *Semin Respir Crit Care Med* 2007 Oct;28(5):496-503

22 Suissa et al. *Arthritis Rheum* 2006 May;54(5):1435-9

equivalent event rates between the TCZ and placebo treatment arms of approximately 0.3 events/100 PY.

7.3.5.5 Malignancies

Malignancies were assessed using preferred terms contained in the Malignant or Unspecified Tumors SMQ Narrow.

Placebo-Controlled Studies

The pooled population of TCZ-treated patients demonstrated a similar rate of malignancy compared to placebo-treated patients, 1.60 events/100 PY (95% CI: 1.04, 2.37) vs. 1.48 events/100 PY (95% CI: 0.74, 2.65). Patients from the MTX-naïve and TNF-IR subpopulations had comparable incidence rates of malignancies to their relevant placebo controls; however, TCZ-treated patients in the DMARD-IR populations demonstrated a numerical difference in malignancy rate vs. their placebo-controlled patients, 1.58 events/100 PY (95% CI: 0.96, 2.44) vs. 0.92 events/100 PY (95% CI: 0.30, 2.15). There were no differences in the type or latency of events between DMARD-IR patients treated with TCZ or placebo. The increased rate of malignancy in the DMARD-IR population could reflect a statistical artifact given the small number of patients, or related to concomitant DMARD therapies which have been implicated in increases of malignancy.

Long-Term Extension Studies

There were a total of 243 events in 215 patients resulting in an incidence rate of 1.62 events/100 PY (95% CI: 1.42, 1.84) in the LTE population. Time to onset of malignancy from initiation of TCZ treatment ranged from eight to 242 days with no clear temporal relationship. The rate of malignancy in the DMARD-IR (1.44 events/100 PY) and MTX-naïve (2.0 events/100 PY) was similar to the all-treated TCZ group (1.62 events/100 PY) while the TNF-IR population was higher at 2.92 events/100 PY. The clinical relevance of the rate in the subpopulations of patients is unclear given the relatively small number of events and patients studied.

To determine that the reported cases of malignancies represented malignancies and not benign tumors, the sponsor conducted a medical review of all reported events and adjudicated each case individually. Tumors were classified as malignant, benign, or other neoplasm (e.g., Bowen's disease) and unknown, which were included in the malignancy category. Based on the review, 194 of the 243 events in the LTE population were confirmed as malignancies (7 were unknown status) for an incidence rate of 1.29 events/100 PY (95% CI: 1.12, 1.49). The most commonly reported malignancies were non-melanoma skin cancer (NMSC; 41 basal cell carcinomas and 24 squamous cell carcinomas). There were 28 cases of lung cancer reported in whom 24 of the patients smoked. Three carcinoid tumors were reported, two gastrointestinal and one pulmonary in origin. Two hepatic neoplasms were reported both of which have been previously reported. Excluding cases of NMSC, the 129 malignancies resulted in a rate of 0.86 events/100 PY). The rates of malignancies (with or without NMSC) are consistent with the rates presented in previous submissions.

Standard Incidence Ratios (SIR) were calculated using the National Cancer Institute's Surveillance Epidemiology End Results (SEER) general population database. For all patient populations (US and non-US) the SIR for all sites of malignancy was greater than one but not statistically significant (Table 13). It should be noted that the rate of malignancies are being compared to the US population but approximately two-thirds of patients are from outside the US where the rate malignancies may be higher. The only site-specific malignancies identified were lung and bronchus tumors in the US population and cervical cancer in non-US patients. For all patients the SIR for lung and bronchus malignancies was 2.06 events/100 PY (95% CI: 1.37, 2.98) and for US patients the rate was 3.32 events/100 PY (95% CI: 1.86, 5.48). Published rates of malignancy in RA patients compared to the general US populations have reported a general increased risk of malignancy (SIR=1.05 [95% CI: 1.01, 1.09]) and specifically for lung cancer (SIR=1.63 [95% CI: 1.43, 1.87]) and lymphoma (SIR=2.09 [95% CI: 1.80, 2.39])¹³.

Table 13. Site-Specific SIRs showing Statistically Significant SIR>1 for the LTE Population

	Observed Cases	Expected Cases	SIR (95% CI)
All Patients (n=4009)			
All sites	129	108	1.19 (0.99, 1.42)
Lung and bronchus	28	14	2.06 (1.37, 2.98)**
US Patients (n=1241)			
All sites	46	34	1.35 (0.99, 1.80)
Lung and bronchus	15	5	3.32 (1.86, 5.48)**
Non-US Patients (n=2768)			
All sites	83	74	1.12 (0.89, 1.39)
Cervical cancer	5	1	4.10 (1.32, 9.57)**

*Excludes NMSC and non-malignant tumors. ** Statistically significant as SIR>1 and 95% CI exclude 1.0. Adapted from sponsor's Clinical Safety Summary, Table 93, page 246.

The overall rate of malignancy in the LTE population was consistent with that expected in the general US population except for the rates of lung and bronchus tumors which were increased in the US population and the rate of cervical cancer in non-US patients. Although the rate of lung and bronchus malignancies were higher than that expected in the general US population, the rates were comparable to those that have been reported in the RA population. The increased rate of cervical cancer in the non-US population may reflect the increased rate of cervical cancer in general outside of the US.

Postmarketing Global Safety Database and Epidemiologic Data

A total of 201 events in 196 patients reported a malignancy during the postmarketing experience for an overall rate estimated to be at least 0.31 events/100 PY (95% CI: 0.27, 0.35). The most commonly reported malignancy in the postmarketing setting was breast cancer (36 events), followed by hematologic malignancies (33 events), GI malignancies (31 events), and lung cancer (22 events). The remaining 79 events included genitourinary malignancies (25 events) and skin malignancies (16 events).

In the MarketScan database, incidence of malignancy rate and in RA patients treated with TNF antagonists was estimated to be 0.45 events/100 PY (95% CI: 0.40, 0.51). These rates are consistent with what have been previously reported in the literature.

In summary, the rate of malignancy in TCZ treated patients was increased compared to placebo-treated patients in the DMARD-IR population but the rates were similar between treatment arms when patient populations were pooled. In the LTE population, the SIR was not statistically different between TCZ and placebo treated patients except for the single-site malignancies of lung and bronchus carcinomas in the US population; however, the overall rate of these malignancies was comparable to published rates for the RA population. In the postmarketing period, the estimated rate of malignancies was consistent to the rates reported in RA patients in general and RA patients treated with TNF antagonists. Overall, the rates and types of malignancies reported in the safety databases are consistent to previous rates and appear to be no greater than the rate seen in the RA population in general or the RA population treated with TNF antagonists.

7.7 Additional Submissions/Safety Issues

7.7.1 4-Month Safety Update

The 4-month safety update was submitted on April 13, 2012 and provides additional LTE data through August 17, 2011 and postmarketing data through October 10, 2011. The additional safety data adds an additional 9,193 PY of exposure to TCZ in the postmarketing global safety database. Overall the additional data did not affect the conclusions drawn from the earlier cutoff of safety data provided for this submission. A brief update of the additional data for SAEs and AE of special interest will be discussed.

Deaths

An additional five deaths from the LTE studies were reported in the 4-month safety update from April 1, 2011 through August 17, 2011. An additional 57 deaths were reported in the postmarketing experience for an overall rate of deaths to be at least 0.42 events/100 PY (95% CI: 0.37, 0.47). This rate is similar to the calculated rate from the initial submission. The most common AEs resulting in death were Infections and Infestations. The data presented in the 4-month safety update are consistent with the data originally submitted to the sBLA 125276/49.

Serious Adverse Events

An additional 83 SAEs were reported during the LTE studies with the most frequently reported SAE being Infections and Infestations. Overall, the SAE profile of TCZ in the postmarketing experience during the 4-month safety update was consistent with the initial analysis. The most frequent SAE during the postmarketing experience was

Infections and Infestations with pneumonia and cellulitis being the most common infections. The rate of SAEs during the 4-month safety update period in the postmarketing setting was estimated to be at least 8.66 events/100 PY (95% CI: 8.45, 8.87), which is comparable to the rate calculated previously (8.30 events/100 PY).

Serious Hepatic Events

There was one serious hepatic event reported in the LTE period. Five additional serious hepatic events and 20 cases of liver enzyme abnormalities (no related reports of serious hepatic events) during the postmarketing period were reported in the 4-month safety update resulting in an estimated incidence rate of at least 0.06 events/100 PY (95% CI: 0.04, 0.07), which is consistent with the rate previously reported. The overall rate of serious liver enzyme/bilirubin elevations during the postmarketing period was estimated to be at least 0.17 events/100 PY (95% CI: 0.14, 0.20), which is also consistent with previous estimates.

Gastrointestinal Perforations

There were 15 additional GI perforations reported in the 4-month safety update during the postmarketing setting resulting in an estimated rate of at least 0.15 events/100 PY (95% CI: 0.12, 0.18), which is the same as the previously calculated rate. One new event was reported during the LTE studies.

Serious Cardiovascular Events

A total of two additional serious MI events, one serious stroke event, and one cardiac death were reported during the 4-month safety update period for the LTE population. In the postmarketing setting, an additional eight serious MI events were reported during the 4-month safety update with an estimated incidence rate of at least 0.09 events/100 PY (95% CI: 0.07, 0.12), which was consistent to the previously calculated rate. Additionally, five additional cardiac deaths were reported during the postmarketing experience in the same time frame resulting in an estimated rate of at least 0.07 events/100 PY (95% CI: 0.05, 0.09), which is consistent with the rate previously reported. An additional eight serious strokes were reported in the 4-month safety update period, which did not effectively alter the incidence rate from the previous calculation. Similarly, 18 cases of serious hypertension and three cases of lipid abnormalities were reported during the 4-month update period, which resulted in estimated incidence rates consistent with previous data.

Hypersensitivity and Anaphylaxis

No new anaphylaxis or serious hypersensitivity reactions were reported in the LTE population during the 4-month safety update. An additional 11 cases of anaphylaxis were reported in the postmarketing experience during the 4-month safety update resulting in an estimated incidence rate of 0.10 events/100 PY (95% CI: 0.08, 0.13), which is consistent with the event rate of anaphylaxis/100 PY with the previous data.

There were no additional deaths due to anaphylaxis reported during the 4-month reporting period. Similarly, there were 12 additional cases of serious hypersensitivity that did not alter the incidence rate compared to the previous rate.

Serious Infections

There were an additional 25 serious infectious events reported in 21 patients for the LTE population during the 4-month safety update period. The most frequently reported AEs were cellulitis, diverticulitis, and pneumonia. During the 4-month safety update period for the postmarketing experience, an additional 296 serious infections reported with the most frequently reported infections being pneumonia, cellulitis, sepsis/septic shock and herpes zoster. The overall estimated rate of serious infections was at least 2.43 events/100 PY (95% CI: 2.32, 2.54) based on an additional 296 serious infections reported in the 4-month safety update. Overall, the rate is higher than the previously calculated rate of 2.31 events/100 PY, which may be attributed to the additional data sources included in the 4-month safety update.

Deaths from Infections

One additional death due to sepsis was reported in the LTE population and 13 additional deaths were reported in the postmarketing experience. Overall the estimated rate of death from infection/100 PY was identical in both populations to the previous calculations. The types of fatal infections were consistent with those previously reported.

Pneumonia

An additional two serious pneumonia cases were reported in the LTE population and an additional 58 cases in the postmarketing experience. The rate for serious pneumonia events for the LTE and postmarketing populations (0.95 events/100 PY and 0.56 events/100 PY) was consistent with that reported in the original submission of this supplement.

Opportunistic Infections

No additional opportunistic infections were reported in the LTE population. An additional 65 events in 63 patients were reported during the postmarketing experience resulting in an estimated rate of 0.09 events/100 PY (95% CI: 0.07, 0.11), which is consistent with what was reported in the original submission of this supplement. The most common serious opportunistic infection was pneumocystis jiroveci pneumonia, which accounted for 32 of the 63 (51%) patients reporting opportunistic infections. Consistent with what was reported with the data originally presented to this supplement, there was a predilection for increased reporting from Japan, which accounted for 44 of the 65 events (68%) resulting in a rate of at least 0.16 events/100 PY in Japan but 0.05 events/100 PY in the ROW region. Overall, the types and rates of opportunistic

infections reported in the 4-month safety update is consistent with the data reported in the original submission of this supplement.

Tuberculosis

One case of TB was reported in the LTE population during the 4-month safety update. In the same update, an additional nine cases of TB reported outside the US in the postmarketing experience for an estimated rate of at least 0.04 events/100 PY (95% CI: 0.02, 0.05), which is consistent with the previous estimated rate.

Neutropenia

No additional cases of neutropenia were reported for the LTE population during the 4-month safety update period. An additional eight cases were reported during the postmarketing period of the 4-month safety update. Three of the cases also reported serious infections within ± 30 days of the neutropenia. None of the infections were fatal. The overall rate of serious neutropenia remained consistent with the rate reported in the original submission of this supplement.

Serious Bleeding and Thrombocytopenia

The LTE population reported an additional three cases of serious bleeding events but no additional cases of thrombocytopenia during the 4-month safety update. In the postmarketing experience, there were an additional 23 reports of serious bleeding events and 14 reports of thrombocytopenia. One report of thrombocytopenia was associated with a case of serious bleeding events. The overall rates of serious bleeding and thrombocytopenia from the LTE and postmarketing experience were consistent with the rates reported in the original submission of this supplement.

Demyelination Events

No new demyelination events were reported in the LTE population and one new event was reported from the postmarketing experience during the 4-month safety update. The rates of demyelination events were consistent with the rates reported in the original submission of this supplement.

Malignancies

A total of six additional malignancies (2 cases of breast cancer, hepatic neoplasm, metastatic neoplasm, lung cancer, pancreatic carcinoma) were reported in the LTE population during the 4-month safety period. A total of 34 additional malignancy events were reported during the postmarketing experience with a resulting estimated incidence rate of at least 0.32 events/100 PY (95% CI: 0.28, 0.36), which is consistent with the rate reported in the original submission of this supplement (0.31 events/100 PY). Overall, the types and rates of malignancies were consistent with the data reported in the original submission of this supplement.

8 Postmarket Experience

Safety data from the postmarketing experience has been extensively reviewed as part of the risk-benefit analyses in this submission. For details, the reader is referred to the Safety section of this review.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

Major labeling changes include

1. Changing of the indication from “*Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonists*” to “*Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatic Drugs*”
2. Modifying language to Section 5.5 Hypersensitivity Reactions, Including Anaphylaxis to read as follows: “*In the postmarketing setting, events of clinically significant hypersensitivity and anaphylaxis, including events with a fatal outcome, have occurred in patients treated with a range of doses of ACTEMRA, with or without concomitant arthritis therapies or premedication. Clinically significant hypersensitivity and anaphylaxis events have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA*”.

Minor labeling changes include modifying language in the label as appropriate to be consistent with the broadened indication.

9.3 Advisory Committee Meeting

As discussed above, a meeting of the Arthritis Advisory Committee was convened on July 29, 2008 to discuss the clinical data in the original tocilizumab BLA submission.

No new Advisory Committee (AC) meeting was deemed necessary for this submission as no issues were identified during the review process to warrant AC discussion.

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/s/

KEITH M HULL
09/10/2012

SARAH K YIM
09/10/2012