



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products

MEMORANDUM

DATE: June 26, 2008

FROM: Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members, and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the July 29, 2008 AAC Meeting to Discuss BLA
125276 for tocilizumab for the treatment of moderately to severely
active rheumatoid arthritis (RA)

Tocilizumab is a recombinant human monoclonal antibody directed against the interleukin-6 receptor. By preventing the binding of interleukin-6 to its receptor tocilizumab inhibits the biological activity of interleukin-6. The clinical development program for tocilizumab included studies of 4 mg/kg and 8 mg/kg and studied tocilizumab monotherapy and tocilizumab use in combination with methotrexate and other disease modifying anti-rheumatic drugs (DMARDs). If licensed, tocilizumab would be the first interleukin-6 inhibitor approved for use in the United States. Tocilizumab is proposed for use at a dose of 8 mg/kg IV every 4 weeks given either as monotherapy or in combination with methotrexate or other DMARDs.

During this meeting, representatives from the Agency and the applicant, Hoffmann-La Roche, Inc., will present:

- the clinical development program for tocilizumab;
- data on the mechanism of action and the clinical pharmacology of tocilizumab, including pharmacokinetic/pharmacodynamic data; and
- data from the clinical trials performed to assess the safety and efficacy of tocilizumab.

Following these presentations, you will be asked to assess these findings and to discuss the apparent risks and benefits of tocilizumab. Several adverse events have been observed in the clinical development program for tocilizumab, including serious infections, malignancies, GI perforations, demyelinating events, liver enzyme abnormalities and elevations in lipid levels. We will ask the committee to address whether the applicant has presented adequate data to determine whether the potential benefits of tocilizumab outweigh the potential risks. We will ask the committee to discuss the appropriate dose of tocilizumab if it is approved. Finally, we will ask the committee what postmarketing studies would be appropriate if tocilizumab is approved.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

BLA 125276 Tocilizumab AAC Items for Discussion

1. Safety of Tocilizumab

A variety of adverse events were observed in the tocilizumab clinical development program, including:

- Serious infections
- Malignancies
- Liver enzyme abnormalities and lipid parameter changes
- Gastrointestinal tract perforations
- Demyelinating disorders

For each of these adverse events, please discuss whether the sponsor has submitted adequate data to make an assessment of its significance for the safety of tocilizumab. In addition, please discuss:

- a) whether the data indicate that the adverse event represents a true safety concern, and;
- b) the potential clinical implications (e.g., with respect to need for monitoring, selection of appropriate patients for treatment, etc.).

2. Appropriate dosing:

Three of the five studies submitted in the application contained data on tocilizumab 4 mg/kg in combination with methotrexate. These data demonstrated a statistically significant increase in the proportion of ACR20 responders in the tocilizumab 4 mg/kg treatment group compared with placebo, although the proportion of patients achieving this response was lower than that observed with the tocilizumab 8 mg/kg treatment group. Regarding safety, the 4 mg/kg dose of tocilizumab appeared to be associated with a lower incidence of serious infection than the 8 mg/kg dose when used in combination with a DMARD; no GI perforation events were reported in patients on 4 mg/kg. In the 24 week controlled period, 3 GI perforations occurred in patients on TCZ 8 mg/kg in vs. none on placebo or 4 mg/kg.

If tocilizumab is approved, discuss what the appropriate dose regimen or regimens should be. Discuss whether there are patients at higher risk of adverse events for whom a lower dose should be recommended.

3. Risk/benefit:

In view of the data available for the safety and efficacy of tocilizumab, discuss whether the benefits outweigh the known and potential risks.

4. Postmarketing studies:

Discuss what postmarketing studies might be important to require of the sponsor if tocilizumab were to be approved.



**Briefing Document for the
Arthritis Advisory Committee Meeting**

July 29, 2008

**Actemra®/Tocilizumab
BLA 125276**

Department of Health & Human Services

**Food & Drug Administration
Center for Drug Evaluation & Research
Division of Anesthesia, Analgesia and Rheumatology Products
Silver Spring, MD 20993**

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Summary of FDA Review of Clinical Efficacy & Safety

Background

Tocilizumab (TCZ) is a recombinant human monoclonal antibody of the IgG1 subclass, directed against the interleukin 6 receptor (IL-6R). By preventing the binding of IL-6 to its receptor, TCZ inhibits the biological activity of IL-6. If approved, TCZ would be the first IL-6 inhibitor approved for use in the United States. The sponsor proposes a dose of 8 mg/kg IV every 4 weeks for the rheumatoid arthritis (RA) indication.

Roche's co-development partner, Chugai Pharmaceutical Co. Ltd., received approval in Japan in April 2005 for the use of tocilizumab in the treatment of multi-centric Castleman's Disease.

The U.S. biologics license application (BLA) is comprised of 5 controlled studies. The key design features of these studies are summarized in Table 1, below. Study WA17822 was conducted entirely outside the US, at 78 centers in 17 countries worldwide. For the remaining studies, US sites were included and US patients comprised 28 to 52% of the total study population. Overall, 440 principal investigators at 593 centers participated in the Roche TCZ RA pivotal studies. No single site or investigator was responsible for more than 3-5% of the study population for a given study.

Table 1: Key Design Features of the 5 Pivotal Phase 3 Studies and the 2 Open-Label Extensions

	WA17822	WA17823	WA17824	WA18062	WA18063	WA18695	WA18696
Design and Duration	DB, R, PC; 24-week	DB, R, PC; year 1 DB, year 2 OL	DB, DD, R, PC; 24-week	DB, R, PC; 24-week	DB, R, PC; 24-week	OL extension study; approximately 5 years*	OL extension study; approximately 5 years*
Patient Population	Moderate to severe active RA in MTX inadequate responders	Moderate to severe active RA in MTX inadequate responders	Active RA; MTX naïve or MTX discontinued but not due to lack of efficacy or toxic effect	Moderate to severe active RA in patients with inadequate response to anti-TNF agent(s)	Moderate to severe active RA in patients with inadequate response to DMARDs	Patients completing treatment in WA17822	Patients completing treatment in WA17824, WA18062, WA18063, WP18663
Treatment	3 arm study: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	3 arm study: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	2 arm study: Tocilizumab: 8 mg/kg iv every 4 weeks or MTX 7.5-20 mg/week (po) Substudy includes 3rd arm: Placebo (8 weeks placebo then 16 weeks TCZ 8 mg/kg)	3 arms: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks plus MTX 10-25 mg/week	2 arms: Tocilizumab: 8 mg/kg or placebo iv every 4 weeks plus standard DMARD(s)	1 arm: Tocilizumab: 8 mg/kg iv every 4 weeks plus MTX	1 arm: Tocilizumab: 8 mg/kg iv every 4 weeks alone or plus MTX / other DMARD(s)
Escape therapy	Week 16: TCZ 8 mg/kg	Week 16 onwards: TCZ 4 or 8 mg/kg	Substudy only, up to Week 8: TCZ 8 mg/kg	Week 16: TCZ 8 mg/kg	Week 16: adjustment of background DMARD	-	-
Total Randomized Patients	623	1196	673	499	1220	537**	1902**
Primary Endpoint at Week 24	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	Long term safety/efficacy	Long term safety/efficacy

DB = double blind, R = randomized, PC = placebo controlled, DD = double dummy, OL = open label

* Or when tocilizumab becomes commercially available in the participating country, or when the sponsor decides to discontinue the study.

** Patients were not randomized into WA18695 and WA18696, but enrolled from studies WA17822, WA18063, WA18062 and WA17824

MTX = methotrexate. Source: Sponsor Table 1 of Module 2.7.3 Summary of Clinical Efficacy

During the course of clinical development, the Agency recommended study of patients with RA on a variety of DMARDs that patients would be likely to take in combination with TCZ if TCZ is approved, including methotrexate, sulfasalazine, azathioprine,

hydroxychloroquine, and leflunomide. Study WA18063 was designed to address this recommendation. The Agency also recommended the sponsor enroll patients completing the controlled studies into open-label long-term extensions to assess the effect of longer-term exposure to TCZ on efficacy and safety parameters. WA18695 and WA18696 were designed for this purpose, and will include approximately 5 years' experience when completed. Interim data from these studies were submitted for the BLA.

Review of Efficacy

Patient Population Characteristics

Table 2 Integrated Summary of Baseline Demographics and Disease Characteristics

Integrated Summary of Baseline Demographics and Disease Characteristics (ITT populations/PP population of WA17824)								
	Pooled DMARD Inadequate Responders*			TNF Inadequate Responders (WA18062)			Early RA (WA17824)	
	Placebo + DMARD** n = 1010	TCZ 4mg/kg + DMARD** n = 612	TCZ 8 mg/kg + DMARD** n = 1406	Placebo + MTX n = 158	TCZ 4mg/kg + MTX n = 161	TCZ 8 mg/kg + DMARD** n = 170	MTX n = 259	TCZ 8 mg/kg n = 265
Gender								
Female	833 (82)	511 (83)	1154 (82)	125 (79)	130 (81)	143 (84)	211 (81)	219 (83)
Male	177 (18)	101 (17)	252 (18)	33 (21)	31 (19)	27 (16)	48 (19)	46 (17)
Age (years)								
mean	52.1	51.4	52.8	53.4	50.9	53.9	50.1	51.1
Height (cm)								
mean	162.7	162.0	162.5	164.8	165.0	164.1	163.0	162.3
Weight (kg)								
mean	73.2	72.1	72.6	75.4	76.4	74.3	72.6	73.4
Race								
White	724 (72)	439 (72)	1008 (72)	150 (95)	144 (89)	152 (89)	188 (73)	187 (71)
Asian	88 (9)	42 (7)	127 (9)	1 (<1)	4 (2)	5 (3)	20 (8)	22 (8)
Native American	69 (7)	41 (7)	116 (8)	2 (1)	3 (2)	1 (<1)	21 (8)	27 (10)
Black	44 (4)	24 (4)	59 (4)	3 (2)	10 (6)	7 (4)	11 (4)	10 (4)
Other	85 (8)	66 (11)	96 (7)	2 (1)	n/a	5 (3)	19 (7)	19 (7)
Ethnicity								
Hispanic	302 (30)	205 (33)	406 (29)	17 (11)	22 (14)	23 (14)	72 (28)	82 (31)
Non-Hispanic	705 (70)	406 (66)	1000 (71)	140 (89)	139 (86)	146 (86)	187 (72)	183 (69)
Not known	1 (<1)	1 (<1)	n/a	1 (<1)	n/a	1 (<1)	n/a	n/a
Duration of RA (years)								
mean	9.0	8.7	9.3	11.4	11.0	12.6	6.3	6.4
Rheumatoid Factor								
negative	234 (23)	123 (20)	281 (20)	40 (25)	44 (27)	36 (21)	65 (25)	67 (25)
positive	776 (77)	489 (80)	1125 (80)	118 (75)	117 (73)	134 (79)	194 (75)	198 (75)
Oral corticosteroids								
Yes	455 (45)	244 (40)	629 (45)	91 (58)	94 (58)	88 (52)	122 (47)	128 (48)
No	555 (55)	368 (60)	777 (55)	67 (42)	67 (42)	82 (48)	137 (53)	137 (52)
Number of Previous DMARDs/TNF inhib								
Mean	1.6	1.7	1.6	2.1	2.0	1.9	1.1	1.2

*Pooled DMARD inadequate responders in studies WA17822, WA17823 and WA18063

**Includes MTX

Adapted from Table 21 of Module 2.7.3, Tables 9 and 10 of WA17824 CSR, and Tables 10 and 11 of WA18062 CSR

As summarized in Table 2 above and Table 3 below, treatment groups within the studies were generally well balanced with respect to baseline demographics, disease characteristics and disease activity.

The majority of patients in the tocilizumab RA pivotal studies were female, Caucasian, and rheumatoid factor (RF) positive, with a mean age in the early fifties. Differences in the target populations between the studies were reflected in disease duration and number of previous DMARDs: WA18062 targeted patients who had a history of active disease

despite TNF inhibitor therapy; these patients had longer disease duration and exposure to a higher number of previous DMARDs. WA17824 targeted patients who were MTX-naive; these patients had shorter disease duration and fewer previous DMARDs.

Baseline disease activity parameters were consistent with the targeted population of RA patients with moderately to severely active disease (Table 3).

Table 3 Integrated Summary of Baseline Disease Activity

Integrated Summary of Baseline Disease Activity (ITT populations/PP population of WA17824)								
	Pooled DMARD Inadequate Responders*			TNF Inadequate Responders (WA18062)			Early RA (WA17824)	
	Placebo + DMARD** n = 1010	TCZ 4mg/kg + DMARD** n = 612	TCZ 8 mg/kg + DMARD** n = 1406	Placebo + MTX n = 158	TCZ 4mg/kg + MTX n = 161	TCZ 8 mg/kg + DMARD** n = 170	MTX n = 259	TCZ 8 mg/kg n = 265
DAS28 (max 10, >5=high) Median	6.7	6.6	6.7	6.8	6.8	6.7	6.8	6.8
Baseline CRP (normal ≤1 mg/dL) Mean	2.4	2.3	2.5	3.7	3.1	2.8	3.0	2.9
Baseline ESR (normal ~15-25 mm/hr) Mean	48.2	47.1	48.1	54.6	51.3	49.1	48.9	49.9
Tender Joint Count (max 68 joints) Mean	29.4	29.8	30.1	30.4	31.3	31.7	31.1	32.2
Swollen Joint Count (max 66 joints) Mean	18.3	18.0	19.0	18.9	19.5	18.9	18.9	19.3
Physician Global (100 mm VAS) Mean	63.3	62.7	63.4	67.5	66.5	66.4	63.2	63.2
Patient Global (100 mm VAS) Mean	64.2	62.6	65.0	70.9	70.4	70.2	65.4	64.0
Patient Pain (100 mm VAS) Mean	57	55.8	57.9	64.1	63.5	64.7	61.3	59.2
HAQ-DI (max 3) Mean	1.5	1.5	1.5	1.7	1.7	1.7	1.5	1.6

*Pooled DMARD inadequate responders in studies WA17822, WA17823, and WA18063

**Includes MTX

Adapted from Table 22 of Module 2.7.3, Table 12 of WA17824 CSR, and Table 13 of WA18062 CSR

Patient Disposition

Table 4 below summarizes the disposition of the patients in the 5 pivotal trials. Overall, a small proportion of patients in each treatment arm discontinued from the studies. Except for Study WA17822, a larger proportion of patients discontinued from the placebo treatment groups. In these studies, a similar proportion of patients discontinued due to adverse events (AE) in the placebo and active treatment arms.

Table 4 Summary of Patient Disposition in the Pivotal RA Studies

Summary of Patient Disposition by Trial and Treatment														
RA Population:	DMARD inadequate			DMARD inadequate			Early RA			TNF inadequate			DMARD inadeq.	
	WA17822			WA17823			WA17824			WA18062			WA18063	
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo* n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population	204	213	205	393	399	398	101	284	288	158	161	170	413	803
Completed	189 (93)	185 (87)	191 (93)	356 (91)	373 (93)	366 (92)	82 (81)	262 (92)	268 (93)	127 (80)	138 (86)	152 (89)	370 (90)	751 (94)
Entered Escape	68 (33)	31 (15)	19 (9)	150 (38)	67 (17)	41 (10)	14 (14)	11 (4)	7 (2)	66 (42)	31 (19)	20 (12)	45 (11)	19 (2)
Total discontinuations	15 (7)	28 (13)	14 (7)	36 (9)	26 (7)	33 (8)	19 (19)	22 (8)	20 (7)	33 (21)	25 (16)	23 (14)	43 (10)	53 (7)
Discontinuation due to AEs	8 (4)	16 (8)	12 (6)	12 (3)	16 (4)	22 (6)	5 (5)	11 (4)	9 (3)	10 (6)	10 (6)	11 (6)	8 (2)	32 (4)
SAEs (other than death)	1	5	4	4	7	3	0	3	2	5	2	3	3	13
Deaths	1	0	0	1	0	0	0	1	3	0	0	0	2	2
Other AE	6	11	8	7	9	19	5	7	4	5	8	8	3	17
Other withdrawals	7 (3)	12 (6)	2 (1)	24 (6)	10 (3)	11 (3)	14 (14)	11 (4)	11 (4)	23 (15)	15 (9)	12 (7)	35 (8)	21 (3)
Insufficient treatment effect	4	3	0	13	2	1	4	3	1	19	6	4	15	3
Protocol violation	1	1	0	2	0	0	2	0	0	0	2	2	3	0
Lost to follow-up	0	1	0	1	1	0	4	1	4	0	4	1	2	2
Patient choice	2	6	1	8	7	9	3	7	6	4	2	4	13	15
Other	0	1	1	1	0	1	1	0	0	0	1	1	2	1

*Placebo controlled substudy

Sources: Fig 2, Tables 6&7; pg 170-171

Fig 2, Tables 6,7,51; pg 164-165

Fig 3, Tables 6&72
sections 3.1.1 & 7.3

Fig 2, Tables 5&6; pg 192

Fig 2, Table 5
section 3.5.2.4

Efficacy Results

The primary endpoint for the studies was the proportion of ACR20 responders at Week 24. As demonstrated in Table 5 below, in each study, a higher proportion of patients achieved ACR20/50/70 responses in the TCZ treatment groups compared with the control groups. Studies WA17822 and WA17823 assessed the effect of TCZ at 4 mg/kg and 8 mg/kg doses compared to placebo add-on therapy in patients who had inadequate response to MTX at 10-25 mg weekly. Study WA18063 investigated the effect of TCZ 8 mg/kg compared to placebo add-on therapy in patients who had inadequate response to a variety of DMARDs, including MTX. Study WA18062 evaluated the effect of TCZ 8 mg/kg and 4 mg/kg compared to placebo add-on therapy in patients who had previously had incomplete response to TNF inhibitor treatment. In each comparison, patients who received TCZ as add-on therapy had a statistically significantly higher rate of response than did patients in the placebo add-on control arms.

Study WA17824 compared TCZ 8 mg/kg monotherapy to methotrexate monotherapy in MTX naïve patients. It was designed as a non-inferiority trial. Patients started on 7.5 mg MTX weekly. At Week 4, if the patient had any swollen or tender joints, the MTX dose was increased to 15 mg. At Week 8, if the patient had any swollen or tender joints, the MTX dose was increased to 20 mg. The pre-specified non-inferiority margin was 12%; that is, non-inferiority would be demonstrated if the lower limit of the 95% confidence interval (CI) of TCZ minus MTX was ≥ -0.12 . The primary analysis utilized the per-protocol population and is displayed in Table 8 below. The results of an analysis using the intent-to-treat (ITT) population were similar to the primary analysis and are displayed

in Table 5. This trial successfully demonstrated the non-inferiority of TCZ compared to MTX. In the event of a demonstration of non-inferiority, the protocol specified a comparison of superiority. The results of this analysis demonstrated that the proportion of ACR20 responders in the TCZ group exceeded the proportion of ACR20 responders in the MTX group, and the difference was statistically significant.

Table 5 Overview of the Percentage of ACR Responders at Week 24, ITT population

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

*Non-inferiority demonstrated if lower limit of 95% CI MRA minus MTX ≥ -0.12 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 19 of WA17822 CSR, Tables 17 & 18 of WA17823 CSR, Tables 17 & 22 of WA17824 CSR

Tables 21 & 23 of WA18062 CSR, and Tables 17 & 20 of WA18063 CSR

The treatment effect of TCZ was further explored in analyses of the proportion of ACR20 responders at Week 24 for patients subgrouped by demographic characteristics, geographic region (Table 6), and disease characteristics (Table 7). Patients from studies WA17822, WA17823 and WA18063 were pooled as these characteristics were similar at baseline for the target population of patients who had active disease despite MTX or other DMARD therapy in these studies.

As shown in Tables 6 and 7 below, treatment with TCZ resulted in a higher proportion of ACR20 responders than did treatment with placebo for all subgroups analyzed. For certain subgroups, for example patients over 75 years of age or patients in the “Other” racial demographic category, the proportion of ACR20 responders in the TCZ 4 mg/kg

group exceeded the proportion of responders in the TCZ 8 mg/kg group. However, the small number of patients in these subgroups precludes definitive conclusions.

Table 6 Subgroup Analyses of the Proportion of ACR20 Responders by Demographic Characteristics and Geographic Region

Subgroup Analyses of the Proportion of ACR20 Responders by Demographic Characteristics and Geographic Region, Pooled DMARD Inadequate Responders in Studies WA17822, WA17823, and WA18063 (ITT Population)						
Subgroup	Placebo + DMARD Total n = 1010 category, n responder, n (%)		TCZ 4 mg/kg + DMARD Total n = 612 category, n responder, n (%)		TCZ 8 mg/kg + DMARD Total n = 1406 category, n responder, n (%)	
Age						
<50 years	390	110 (28)	390	110 (28)	484	314 (65)
50-64 years	457	122 (27)	241	115 (48)	685	385 (56)
65-75 years	140	25 (18)	92	45 (49)	212	124 (58)
>75 years	23	4 (17)	9	5 (56)	25	9 (36)
Race						
Native American	69	25 (36)	41	26 (63)	116	81 (70)
Asian	88	19 (22)	42	17 (40)	127	75 (59)
Black	44	11 (25)	24	10 (42)	59	29 (49)
White	724	181 (25)	439	211 (48)	1008	591 (59)
Other	85	25 (29)	66	40 (61)	96	56 (58)
Gender						
Female	833	215 (26)	511	250 (49)	1154	686 (59)
Male	177	46 (26)	101	54 (53)	252	146 (58)
Weight						
<60 kg	252	64 (25)	160	88 (55)	345	223 (65)
60-100 kg	667	177 (27)	405	205 (51)	951	555 (58)
>100 kg	87	18 (21)	43	11 (26)	104	52 (50)
BMI						
<18.5	31	9 (29)	16	8 (50)	44	31 (70)
18.5-24.9	347	85 (24)	225	125 (56)	496	310 (62)
25-29.9	340	94 (28)	198	90 (45)	454	268 (59)
≥30	287	71 (25)	167	80 (48)	403	220 (55)
Geographic Region						
North America	309	73 (24)	128	53 (41)	489	234 (48)
So/Cen America	229	82 (36)	155	89 (57)	318	220 (69)
Europe	357	85 (24)	258	126 (49)	438	283 (65)
Rest of World	115	21 (18)	71	36 (51)	161	95 (59)

Adapted from Tables etsumacr20poolwk241-246 of Module 2.7.3 Summary of Clinical Efficacy

Table 7 Subgroup Analyses of the Proportion of ACR20 Responders by Disease Characteristics

Subgroup Analyses of the Proportion of ACR20 Responders by Disease Characteristics, Pooled DMARD Inadequate Responders in Studies WA17822, WA17823, and WA18063 (ITT Population)						
Subgroup	Placebo + DMARD Total n = 1010 category, n responder, n (%)		TCZ 4 mg/kg + DMARD Total n = 612 category, n responder, n (%)		TCZ 8 mg/kg + DMARD Total n = 1406 category, n responder, n (%)	
Disease Duration						
≤2 yrs	208	62 (30)	109	64 (59)	274	163 (59)
>2 to ≤5 yrs	201	52 (26)	136	70 (51)	289	179 (62)
>5 to ≤10 yrs	251	61 (24)	157	85 (54)	325	192 (59)
>10 yrs	350	86 (25)	210	85 (40)	517	298 (58)
RF status						
Positive	776	201 (26)	489	253 (52)	1125	687 (61)
Negative	234	60 (26)	123	51 (41)	281	145 (52)
Baseline DAS28						
<Median	529	139 (26)	325	168 (52)	692	404 (58)
≥Median	469	121 (26)	281	134 (48)	703	427 (61)
Baseline CRP (mg/dL)						
<0.3	101	27 (27)	*	*	152	72 (47)
≥0.3 to <1	323	79 (24)	*	*	385	217 (56)
≥1 to <3	328	84 (26)	*	*	471	271 (58)
≥3 to <10	229	64 (28)	*	*	352	240 (68)
≥10	29	7 (24)	*	*	46	32 (70)
Oral Corticosteroids						
Yes	613	175 (29)	392	198 (51)	779	481 (62)
No	397	86 (22)	220	106 (48)	627	351 (56)
Number of Previous DMARDs						
0	262	82 (31)	122	62 (51)	373	220 (59)
1	306	86 (28)	213	118 (55)	407	249 (61)
2	207	51 (25)	142	72 (51)	305	196 (64)
3	119	23 (19)	72	37 (51)	166	93 (56)
>4	116	19 (16)	63	15 (24)	155	74 (48)

*Analysis not provided

Adapted from Tables 60 and etsumacr20poolwk248-2413 of Module 2.7.3 Summary of Clinical Efficacy

Sensitivity Analyses of the Primary Endpoint, Percentage of ACR20 Responders

The primary analysis for 4 out of the 5 studies (excepting WA17824, which was a non-inferiority comparison) was the comparison of the proportion of ACR20 responders in the TCZ 8 mg/kg + DMARD treatment group vs. the placebo + DMARD group, using the ITT population. Missing data (i.e., due to patient discontinuation or escape, or insufficient ACR core variables to calculate the ACR20) were handled using a nonresponder imputation.

To explore the effect of the specified imputation technique on the study results, sensitivity analyses were conducted using other imputation techniques. The sponsor performed a sensitivity analysis utilizing last-observation-carried forward (LOCF) for missing ACR core variables. FDA conducted an additional analysis utilizing baseline-observation-carried forward (BOCF) for missing ACR core variables. Table 8, below, illustrates the difference in outcomes using these different imputation techniques. Results of these sensitivity analyses are consistent with the results of the primary analysis.

The primary analysis for WA17824 was a non-inferiority comparison of TCZ 8 mg/kg monotherapy vs. placebo for the per-protocol population. The per-protocol population

included all patients in the ITT population who adhered to the protocol. For the primary method of analysis, no imputation of missing post-baseline values was performed for the physician global, patient global, patient pain VAS, HAQ-DI scores, or acute phase reactants; LOCF was used to derive tender joint counts (TJC) or swollen joint counts (TJC) if missing. As a sensitivity analysis, LOCF was utilized for any missing ACR core variables; results were consistent with the primary analysis. An additional sensitivity analysis was performed utilizing the ITT population with LOCF for missing ACR core variables. Again, results were very similar to results obtained from the primary analysis.

Table 8 Sensitivity Analyses of the Primary Endpoint

Sensitivity Analyses of the Primary Endpoint, Percentage of Patients with ACR20 Response at Week 24					
Study	Pbo + DMARD**	TCZ 4mg/kg + DMARD**	TCZ 8mg/kg + DMARD**	p-value (4 mg/kg)	p-value (8 mg/kg)
Patients with incomplete response to MTX or other DMARDs, ITT Population					
WA17822	(n=204)	(n=213)	(n=205)		
Primary Analysis	26	48	58	<0.0001	<0.0001
LOCF of ACR Components	27	53	60	<0.0001	<0.0001
BOCF of ACR Components	27	49	59	<0.0001	<0.0001
WA17823	(n=393)	(n=399)	(n=398)		
Primary Analysis	27	51	56	<0.0001	<0.0001
LOCF of ACR Components	29	54	60	<0.0001	<0.0001
BOCF of ACR Components	28	51	57	<0.0001	<0.0001
WA18063	(n=413)		(n=803)		
Primary Analysis	24		61		<0.0001
LOCF of ACR Components	26		64		<0.0001
BOCF of ACR Components	24		61		<0.0001
Patients with incomplete response to prior TNF inhibitor treatment, ITT Population					
WA18062	(n=158)	(n=161)	(n=170)		
Primary Analysis	10	30	50	<0.0001	<0.0001
LOCF of ACR Components	13	35	54	<0.0001	<0.0001
BOCF of ACR Components	11	31	51	0.1005	0.0002
MTX naïve/Early RA patients, Non-Inferiority Assessment					
Study	MTX	TCZ 8 mg/kg	Tx Diff	95% CI	
WA17824	PP n = 259 ITT n = 284	PP n = 265 ITT n = 286			
Primary Analysis (PP Pop)	52	71	0.21	(0.13,0.29)*	
LOCF (PP Pop)	55	72	0.20	(0.12,0.29)	
ITT Analysis	52	70	0.19	(0.11,0.27)	

*Non-inferiority demonstrated if lower limit of 95% CI MRA minus MTX \geq -0.12 for primary analysis population

**DMARD = MTX for WA17822, 17823 and WA18062; includes MTX and other DMARDs in WA18063

Sources: Tables 17 & 18 of WA17822 CSR, Tables 17 & p. 677 of WA17823 CSR, Tables 16, 17 and p.757 of WA17824 CSR

Tables 21 & 22 of WA18062 CSR, and Tables 17 & 18 of WA18063 CSR.

BOCF analyses performed by FDA Statistician, Dr. Joan Buenconsejo

Consistent with the overall results, treatment with TCZ resulted in improvement in all ACR components at Week 24 (see Appendix, Table 30). Additional analyses were performed by the FDA statistician, Dr. Joan Buenconsejo, evaluating the cumulative responder profile for each study and the proportion of ACR20 and ACR50 responders by week of study. The results of these analyses are also consistent with the conclusion that TCZ treatment is effective in RA, and are displayed on pages 32-34 of this briefing document.

Review of Safety

Discussion of Clinical Studies Used to Evaluate Safety

This submission contained 24-week safety data from 5 pivotal trials (Table 1, above), including 6-month interim data from WA17823, which is designed as a 2-year study. These studies were of sufficiently similar design to allow for pooled analyses of the 6-month controlled data, by treatment group.

Long-term safety information from RA patients treated with open-label TCZ 8 mg/kg was also provided in this summary. The data are derived from two-open label extension studies, WA18695 and WA18696, which are ongoing. The clinical cut-off date for the provision of data from the extension study program was April 20th, 2007, with updated data through October 1, 2007 submitted in the 120-day safety update.

Additional safety information was provided for adverse events of interest from studies in the Chugai clinical development program in RA and other indications up to a clinical cut-off date of August 31st, 2007. (See appendix, Table 31).

Deaths and SAEs occurring through January 31, 2008 from the ongoing Chugai development program, post-marketing spontaneous reports from the treatment of multicentric Castleman's Disease (approved in Japan), compassionate use of TCZ in children with systemic juvenile idiopathic arthritis (SJIA), the ongoing study WA17823, and the ongoing extension studies WA18695 and WA18696, were submitted in the 120-day safety update.

Table 9 Summary of Exposure to TCZ

Exposure in the Roche Tocilizumab RA Pivotal Studies and Long-Term Extensions		
Population	Number of patients	Duration TCZ exposure (patient-yrs)
6 mo safety population, all TCZ	2644	1131
Pooled Long Term Extensions	2562	3685
All Exposure	3778	4142
≤ 3 months	3474	799
≤ 6 months	3183	1464
≤ 12 months	2121	1951
≤ 18 months	1463	2019
≤ 24 months	640	1178
≤ 30 months	113	260
Total exposure, TCZ 4 mg/kg	1181	435
Total exposure, TCZ 8 mg/kg	3242	3707

Source: Table 3 and 4 of 120 day safety update, data cut-off Oct. 1, 2007

As shown in Table 9 above, almost 3800 patients have been exposed to TCZ in the Roche RA program. An additional 1600 patients have been exposed to TCZ in the supportive studies. The majority of TCZ exposure has been to the higher dose of 8 mg/kg.

Safety overview

The majority of patients in the TCZ RA pivotal studies experienced at least one adverse event (AE) during the course of the trial. The proportion of patients experiencing an adverse event in the TCZ treatment arms was similar to the proportion of patients experiencing an adverse event with MTX monotherapy, and was higher than with placebo.

Deaths were uncommon, but were observed in all treatment arms during the 6-month controlled period, except in the TCZ 4 mg/kg treatment arm. The highest proportion of deaths (3/288, 1%) occurred in the TCZ 8 mg/kg monotherapy arm of Study WA17824. Exposure-adjusted incidence of deaths and serious adverse events (SAE) are discussed in further detail in the next section.

The proportion of patients experiencing an AE leading to withdrawal was small (<5%) in each treatment group but was lowest with placebo. During the double-blind controlled portion of the studies, dose modification entailed temporary withholding of a scheduled dose, e.g., for the first occurrence of AST/ALT elevation >3 X ULN, or for non-serious infections. Background DMARD therapy doses could be modified for toxicity and WA17824 specified scenarios for MTX modification in the protocol. Dose reduction from TCZ 8 mg/kg to TCZ 4 mg/kg was allowed in the long-term extensions for safety reasons, such as AST/ALT elevation or decreased WBC (see Tables 23 and 24, below).

Table 10 Overview of AEs and Deaths in the Tocilizumab RA Pivotal Studies and Long-Term Extensions

	Overview of AEs and Deaths in the Tocilizumab RA Pivotal Studies and Long-Term Extensions						Long term safety population Pooled TCZ
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	
Enrolled	1170	284	774	1582	288	2644	2562
Pts with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Deaths	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)
Pts with SAEs	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Pts with AEs leading to withdrawal	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Pts with AEs leading to dose modif.	84 (7)	63 (22)	103 (13)	194 (12)	56 (19)	353 (13)	884 (34)

*Includes MTX

AE=adverse event, SAE=serious adverse event

Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population

Adapted from Table 15 of Module 2.7.4 and Table 5 of 120 day safety update

Exposure adjusted incidence of deaths, SAEs, SIEs, and malignancies

In the placebo-controlled portion of the trials, patients could escape at Week 16 if they had an inadequate response. In general, a higher proportion of patients in the placebo treatment groups entered escape (see Table 4, above). Thus the overall exposure time of

patients to placebo was shorter than the designated 6 months. Conversely, the majority of patients in the long-term safety population have been exposed to TCZ treatment for at least 1 year (see Table 9, above). To account for these differences in exposure for comparison by treatment arms, exposure adjusted incidence rates were calculated for deaths, SAEs, serious infectious events (SIE), and malignancies, summarized in Table 11, below.

Table 11 Exposure Adjusted Incidence Rates of Deaths, SAEs, SIEs, and Malignancies

Exposure and Exposure Adjusted Incidence Rates for Deaths, SAEs, SIEs, and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions							
	6-months pooled safety population						Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patient-years exposure	462	123	321	685	126	1131	3685
Deaths, n (%)	4 (0.3)	1 (0.4)	0	2 (0.1)	3 (1)	5 (0.2)	16 (0.6)
Deaths per 100 pt-yrs	0.9	0.8	0	0.3	2.4	0.4	0.4
Malignancies, n (%)	7 (0.6)	3 (1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	60 (2.3)
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6
No. with ≥1 SAE, n (%)	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Number of SAE	74	15	51	115	12	178	489
SAEs per 100 pt-yrs	16	12	16	17	10	16	13
No. with ≥1 SIE, n (%)	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)
Number of SIE	18	2	15	39	4	58	141
SIEs per 100 pt-yrs	3.9	1.6	4.7	5.7	3.2	5.1	3.8

* Includes MTX

Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population

Adapted from Tables 12, 13, 24, 27 and 38 of Module 2.7.4 Summary of Clinical Safety and source tables STae_py_mal and SStrate_ae_s; and tables 4, 5, 9, 20 and stae11_sl of 120 d safety update; p.5 of Amendment 14

Overall, the exposure-adjusted incidence rates of death were not elevated in the TCZ treatment groups compared to the placebo or MTX monotherapy treatment groups, with the exception of the TCZ 8 mg/kg monotherapy treatment group (1% or 2.4/100 pt-yrs compared to 0.3% or 0.9/100 pt-years with placebo). This finding is difficult to interpret because of the small number of deaths involved, namely 3 among 288 patients receiving TCZ 8 mg/kg monotherapy. In addition, if TCZ 8 mg/kg were truly associated with a higher risk of death, it is surprising that TCZ 8 mg/kg in combination with DMARDs does not also show a higher rate of death. Finally, to provide perspective for the death rate in the TCZ 8 mg/kg monotherapy group, we compared the rate to that seen in published studies of mortality in patients with RA. These analyses showed that the exposure-adjusted rate of 2.4 deaths per 100 patient-years in this group is similar to expected in the RA population based on published mortality rates. For example, in the Olmsted County RA cohort, death rates for female and male RA patients between 1965 and 2005 were relatively constant at 2.4 and 2.5 deaths per 100 person-years, respectively [Gonzalez 2007].

The exposure-adjusted incidence rate of malignancies, including non-melanoma skin cancers, was similar in all treatment groups at 1.5 to 1.6 malignancies per 100 patient-years, with the exception of a slightly higher rate of 2.4 malignancies per 100 patient-

years observed in the MTX monotherapy group. If non-melanoma skin cancers are excluded, TCZ treatment group malignancy rates range from 0.8 to 1.2 (long-term safety population) malignancies per 100-patient-years, compared to 0.9 for the placebo-treatment group. These rates are comparable to published malignancy rates from RA patient cohorts:

- National Data Bank for Rheumatic Diseases [Wolfe/Michaud, 2007], 1 non-cutaneous malignancy per 100 patient-years;
- Danish Cancer Registry [Mellemkjaer 1996], 1.3 malignancies per 100 patient-years;
- British Society for Rheumatology Biologics Register (BSRBR), 0.8 to 1.4 malignancies per 100 patient-years

When segmented by age groups and compared to the NCI Surveillance Epidemiology and End Results (SEER) general population database (Table 12, below), RA patients in the Roche Tocilizumab program had a higher incidence of malignancy than would be expected in the U.S. general population. As a caveat, it should be noted that of the total study population in the 5 pivotal studies, 2/3 were from outside the U.S.

Table 12 Malignancy Incidence Rates Compared to SEER Database

Malignancy Incidence Rates in Roche Tocilizumab RA Program, Excluding Non-Melanoma Skin Cancers, Compared to SEER Database General Population and Segmented by Age Groups									
	Combined			Female			Male		
	No. reported	Observed rate per 100 pt-yr	SEER rate per 100 pt-yr	No. reported	Observed rate per 100 pt-yr	SEER rate per 100 pt-yr	No. reported	Observed rate per 100 pt-yr	SEER rate per 100 pt-yr
Total	42	1.02		30			12		
30-34 year olds									
All sites	1	0.593	0.081	1	0.701	0.101	-	-	0.062
Lung	1	0.593	0.001	1	0.701	0.001	-	-	0.001
35-39 year olds									
All sites	-	-	0.125	-	-	0.162	-	-	0.089
40-44 year olds									
All sites	1	0.254	0.207	1	0.298	0.268	-	-	0.146
45-49 year olds									
All sites	2	0.372	0.342	2	0.468	0.410	-	-	0.272
Cervix Uteri	-	-	-	1	0.234	0.015	-	-	-
Breast	-	-	-	1	0.234	0.187	-	-	-
50-54 year olds									
All sites	3	0.438	0.551	2	0.350	0.571	1	0.882	0.530
Cervix Uteri	-	-	-	1	0.175	0.014	-	-	-
Ovary	-	-	-	1	0.175	0.022	-	-	-
Prostate	-	-	-	-	-	-	1	0.882	0.138
55-59 year olds									
All sites	11	1.535	0.876	5	0.856	0.800	6	4.515	0.956
Corpus Uteri	-	-	-	2	0.342	0.067	-	-	-
Breast	-	-	-	2	0.342	0.308	-	-	-
Lung	4	0.557	0.107	-	-	0.092	4	3.006	0.123
Prostate	-	-	-	-	-	-	1	0.749	0.335
Stomach	2	0.278	0.012	1	0.171	0.008	1	0.748	0.017
60-64 year olds									
All sites	9	1.775	1.291	8	2.056	1.062	1	0.848	1.542
Cervix Uteri	-	-	-	1	0.256	0.015	-	-	-
Breast	-	-	-	1	0.256	0.364	-	-	-
Lung	4	0.786	0.191	3	0.768	0.158	1	0.848	0.226
NHL	1	0.196	0.063	1	0.256	0.055	-	-	0.073
65-69 year olds									
All sites	7	1.951	1.796	6	2.200	1.372	1	1.162	2.289
Cervix Uteri	-	-	-	1	0.365	0.015	-	-	-
Colon/Rectal	1	0.278	0.185	1	0.365	0.152	-	-	0.224
Lung	2	0.555	0.291	2	0.730	0.238	-	-	0.352
70-74 year olds									
All sites	7	4.059	2.170	5	3.539	1.624	2	6.415	2.856
Colon/Rectal	1	0.572	0.246	1	0.703	0.202	-	-	0.301
Lung	1	0.572	0.382	1	0.702	0.305	-	-	0.479
Stomach	1	0.572	0.038	1	0.703	0.025	-	-	0.055
75-79 year olds									
All sites	1	1.228	2.453	-	-	1.883	1	9.378	3.266
Colon/Rectal	1	1.228	0.316	-	-	0.273	1	9.378	0.379

18 non-melanoma skin cancers excluded, as they are not collected by SEER; 4135 person-years

All sites number includes malignancies of gammopathy, glioblastoma, metastatic neoplasm, metastatic squamous cell carcinoma and thyroid neoplasm

Data cut-off October 1, 2007; adapted from Table 2, BLA 125276 amendment 14

A similar incidence of serious adverse events was noted in the TCZ treatment groups compared to placebo. TCZ and MTX monotherapy groups had the lowest exposure-adjusted incidence (10 and 12 events per 100 patient-years, respectively). The rate of serious adverse events did not increase with increasing duration of TCZ exposure observed in the long-term safety population.

The incidence rate of serious infections was highest in the TCZ 8 mg/kg + DMARD combination treatment group at 5.7 SIEs per 100 patient-years, and was slightly lower in the TCZ 4 mg/kg + DMARD group at 4.7 SIEs per 100 patient-years. Both rates exceeded the observed rate of 3.9 events per 100 patient-years in the placebo + DMARD group. TCZ and MTX monotherapy groups again had the lowest exposure-adjusted incidence with 3.2 and 1.6 SIEs per 100 patient-years, respectively. The rate of SIEs did not increase with increasing duration of TCZ exposure in the long-term safety population (3.8 SIE per 100 pt-years). Rates of serious infections in RA patients taking TNF inhibitors have been published as approximating 5-6 SIEs per 100 patient-years, compared to 2-4 SIE per 100 patient-years in RA patients taking non-biologic DMARDs [Listing 2005, Dixon 2007].

Deaths

During the TCZ RA pivotal studies and long-term extensions to date, five patients died of cardiac etiologies (4 myocardial infarctions and 1 cardiac failure) and four patients died of infectious etiologies while on TCZ treatment. A line listing of deaths in the Roche TCZ pivotal studies and long term extensions may be found in Table 13, below. Other deaths in the TCZ global program are described in Table 32 in the appendix. Overall, the numbers and causes of deaths in the program appear to be consistent with what might be expected for the underlying patient population.

Nonfatal Serious Adverse Events: Malignancy

As discussed above, the overall exposure-adjusted incidence of malignancy in the TCZ RA studies appears to be within the range of what might be expected in the RA patient population. The types of malignancies observed are described in Table 14, below. Few malignancies were observed during the 6-month controlled period of the RA pivotal studies. During the long-term extensions, a total of 65 neoplasms or malignancies were diagnosed; basal cell skin carcinomas occurred most commonly, followed by lung neoplasms and lung cancers. The published literature is consistent in suggesting an increased risk of non-melanoma skin cancers in RA patients; for lung cancer, the relative risk for RA patients is less certain, although lung cancer is the one of the most common cancers in the general population (2nd most frequently diagnosed in both Caucasian men and women, 1988-1992, SEER). The relative risk of lymphoma is higher in RA patients, however thus far, only a single case of lymphoma has occurred with TCZ treatment in Roche RA program. Overall, the pattern and frequency of malignancies observed in the TCZ RA program to date appears consistent with what might be expected in RA patients and does not clearly implicate an additional risk attributable to TCZ treatment.

Table 13 Deaths in the TCZ RA Pivotal Studies and Long-Term Extensions

Line Listing of Deaths in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment				
Tx Grp/Pt no.	Age/sex	Last tx day	Day of death	Cause of death
Placebo + DMARD (n = 1170)				
3298	46/M	84	101	Coronary artery thrombosis
5633	55/F	1	103	Wegener's Granulomatosis
7737	55/F	113	140	Pneumonia
6937	68/F	85	135	Intestinal obstruction
MTX (n = 284)				
4141	71/M	119	177	Lung neoplasm malignant
TCZ 8mg/kg + DMARD (n = 1582)				
7722	48/F	113	120	Hemorrhagic stroke, aneurysm rupture
6713	75/F	27	54	Post procedural complication
TCZ 8 mg/kg (n = 288)				
4013	46/F	142	150	Ischemic necrosis of AV node
4221	76/F	29	37	GI hemorrhage
4929	50/F	36	40	Myocardial ischemia
Pooled TCZ long-term extensions (n = 2562)				
3440	73/F	452	534	Gastric cancer
3739	71/F	169	183	Acute myocardial infarction
7328	72/F	229	393	Bacterial bronchitis
6554	63/M	30	47	Suicide
6981	58/F	338	420	Septic shock
8888	75/F	251	268	Pneumonia
5421	59/F	218	472	Diverticular perforation
5423	63/F	225	234	Beta hemolytic strep infection
5883	67/M	336	341	Myocardial infarction
5326	68/F	112	203	Progressive idiopathic polyneuropathy
5151	83/F	78	100	Unknown
3070	70/F	255	357	Metastatic colon cancer
6288	70/M	414	441	Acute renal failure
7366	45/F	473	477	Suicide
5687	57/F	351	372	Myocardial infarction
4943	70/F	169	200	Cardiac failure

Adapted from Table 20 of Module 2.7.4 and Table 6 of 120 day safety update (cut-off date October 1, 2007)

Table 14 Neoplasms and Malignancies

Neoplasms and Malignancies in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Type and Trial Treatment							
	6-months pooled safety population						Long term
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	safety population Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients with ≥1 AE	7 (0.6)	3 (1.1)	5 (0.6)	10 (0.6)	2 (0.7)	17 (0.6)	65 (2.5)
Total neoplasms and malignancies	7	3	6	10	2	18	65
Malignancies per 100 pt-yrs	1.5	2.4	1.6	1.5	1.6	1.5	1.6
Solid Tumors							
Lung neoplasm	1	-	1	2	-	3	9
Lung cancer	-	1	1	-	-	1	7
<i>Small cell, stage unsp.</i>	-	-	-	-	-	-	2
<i>Adenocarcinoma</i>	-	-	-	-	-	-	2
<i>Squamous cell</i>	-	-	-	-	-	-	1
<i>Non-small cell</i>	-	-	-	-	-	-	1
<i>Not specified</i>	-	1	1	-	-	1	1
Thyroid neoplasm	-	-	-	1	-	1	6
Breast cancer, including in situ	1	-	-	-	-	-	4
Squamous cell carcinoma, unsp	-	-	-	1	-	1	3
Cervical cancer	-	-	1	-	-	1	3
Gastric cancer	-	-	-	-	1	1	2
Prostate cancer	1	-	-	-	-	-	2
Colon or rectal cancer	1	1	-	1	-	1	2
Colon neoplasm	-	-	-	-	-	-	1
Adrenal neoplasm	-	-	-	-	-	-	1
Endometrial neoplasm	-	-	-	-	-	-	1
Glioblastoma	-	-	-	-	-	-	1
Meningeal neoplasm	-	-	-	1	-	1	1
Metastatic neoplasm	-	-	-	-	-	-	1
Ovarian cancer	-	-	-	-	-	-	1
Uterine cancer	-	-	-	1	-	1	1
Hepatic neoplasm	-	-	1	-	-	1	-
Non-melanoma skin CA							
Basal cell carcinoma	1	-	-	1	1	2	12
Bowen's disease	-	-	1	1	-	2	3
Neoplasm, skin	-	-	-	-	-	-	1
Carcinoma in situ, skin	-	-	-	-	-	-	1
Dysplastic nevus syndrome	1	-	-	-	-	-	-
Squamous cell CA, skin	1	-	-	1	-	1	-
Skin cancer, NOS	-	-	1	-	-	1	-
Hematologic/Lymphatic							
Diffuse large B-cell lymphoma	-	-	-	-	-	-	1
Gammopathy	-	-	-	-	-	-	1
T cell lymphoma	-	1	-	-	-	-	-

* Includes MTX

Data cut-off April 20, 2007 for 6 month pooled safety population; October 1, 2007 for long-term safety population

Adapted from source table STae11_mal of Module 2.7.4 Summary of Clinical Safety, Table 20 of 120 d safety update

Serious Infections

TCZ treatment was associated with a higher risk of serious infections. The numbers and types of serious infections are shown in Table 15, below. Of these, pneumonia and cellulitis were by far the most commonly occurring serious infections. In addition to commonly occurring bacterial infections, treatment with TCZ was associated with an increased incidence of herpes zoster, including herpes zoster ophthalmicus. No other viral reactivation events were noted in the Roche RA program, however a single case of serious EBV reactivation complicated by non-Hodgkin's lymphoma and resulting in death was observed in the Chugai RA trials. Patients with a history of recurrent

infections, including hepatitis B, hepatitis C, and herpes zoster were excluded from the RA trials.

Patients were also excluded from the studies if they had a history of or known active mycobacterial infections, but were not specifically required to have TB screening or prophylaxis; in fact, 53 patients had a history of TB or positive PPD prior to study start. Despite this and the global nature of the studies, only a single case of TB has been diagnosed in the program thus far. Additionally, two opportunistic infections were diagnosed: one case of pneumocystis jiroveci pneumonia and one case of mycobacterium avium intracellulare pneumonia.

Thus far, the overall safety profile of TCZ with respect to infections is consistent with that of other immunosuppressants and implicates an increased risk of serious infection with TCZ treatment.

Serious Adverse Events

The numbers and types of SAE are displayed in Table 16, below. Serious infections were the most common type of serious adverse event, followed by the gastrointestinal (GI) disorder and injury system-organ classes (SOC). The injury SOC was primarily populated by events of falls and fractures. GI events included GI perforations, which are discussed in greater detail below.

The overall rate of myocardial infarctions (MI) in the RA Phase 3 studies and long term extensions remained consistent over time (data not shown). As of the final data cut-off for the 120-day safety update (January 31, 2008 for deaths and SAE), 15 MI were diagnosed in approximately 4158 patient-years exposure for a rate of 0.35 per 100 patient-years. This rate is not elevated compared to published rates of MI in RA patients, which range from 0.47 per 100 patient-years in the ARAMIS database to 0.76 per 100 patient-years in the National Data Bank for Rheumatic Diseases.

Similarly, the rate of cerebrovascular accident events in patients treated with TCZ during the Phase 3 studies is not elevated compared to published rates. Nine CVA were diagnosed in 4158 patient-years exposure for a rate of 0.22 per 100 patient years. Note that Table 16 does not list two of the events: two patients who remain on blinded treatment in WA17823 (designed as a 2 year study). Published rates range from 0.11 per 100 patient-years in female RA patients within the Nurse's Health Study to 0.76 per 100 patient-years in the UK General Practice Research database.

Table 15 Serious Infections

Serious Infectious Events (SIE) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment							
	6-months pooled safety population					Long term	
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	safety population Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients with ≥ 1 SIE	17 (1.4)	2 (0.7)	13 (1.7)	38 (2.4)	4 (1.4)	55 (2.1)	133 (5.2)
Total number of SIEs	18	2	15	39	4	58	141
SIEs per 100 pt-years	3.9	1.6	4.7	5.7	3.2	5.1	3.8
Infections-pathogen unspecified							
Total patients with at least one AE	17 (2)	2 (1)	12 (2)	18 (1)	4 (1)	34 (1)	90 (4)
Pneumonia	4	1	5	9	2	16	35
<i>Pneumonia, empyema or necrotizing</i>	-	-	1	1	-	2	1
Abscess	4	-	-	2	-	2	9
<i>Intra-abdominal</i>	1	-	-	1	-	1	2
<i>Soft-tissue</i>	2	-	-	-	-	-	5
<i>Oral</i>	1	-	-	-	-	-	1
<i>Peri-anal</i>	-	-	-	1	-	1	1
Gastroenteritis/Diarrhea	-	-	3	-	-	3	8
Respiratory tract infection	1	-	2	2	-	4	7
Diverticulitis	-	-	-	-	-	-	6
Urinary tract infection	5	-	1	3	-	4	5
<i>Pyelonephritis</i>	1	-	-	2	-	2	2
Sepsis	1	1	2	1	-	3	4
<i>Pulmonary sepsis</i>	-	-	-	-	-	-	1
<i>Urosepsis</i>	1	-	-	-	-	-	1
Skin/soft tissue/nail	-	-	-	-	-	-	4
Osteomyelitis	2	-	1	-	-	1	3
Sinusitis	-	-	-	-	1	1	2
Appendicitis	-	-	-	-	-	-	2
Arthritis/tenosynovitis, infective	-	-	-	-	-	-	2
Wound/post-procedural infection	-	-	-	-	-	-	2
Cholecystitis, acute	-	-	-	-	-	-	1
Otitis media or externa	-	-	-	1	-	1	1
Gingival infection	-	-	-	-	-	-	1
Intervertebral discitis	-	-	-	-	-	-	1
Meningitis, aseptic	-	-	-	-	-	-	1
Mediastinitis	-	-	-	1	-	1	-
Sialoadenitis	-	-	-	-	1	1	-
Bacterial Infectious Disorders							
Total patients with at least one AE	1 (<1)	0	0	15 (1)	0	15 (1)	34 (1)
Cellulitis	1	-	-	11	-	11	21
<i>Cellulitis, gangrenous</i>	-	-	-	-	-	-	1
<i>Staphylococcal cellulitis</i>	-	-	-	1	-	1	-
<i>Erysipelas</i>	-	-	-	1	-	1	2
Bacterial arthritis	-	-	-	2	-	2	3
<i>Staph septic arthritis</i>	-	-	-	1	-	1	-
Enterococcal endocarditis	-	-	-	1	-	1	-
Pneumococcal pneumonia	-	-	-	1	-	1	2
Beta hemolytic strep	-	-	-	-	-	-	1
Bacterial bronchitis	-	-	-	-	-	-	1
C. Difficile colitis	-	-	-	-	-	-	1
Helicobacter gastritis	-	-	-	-	-	-	1
Salmonellosis	-	-	-	-	-	-	1
E. Coli UTI	-	-	-	-	-	-	1
Streptococcal infection NOS	-	-	-	-	-	-	1
Staphylococcal infection NOS	-	-	-	-	-	-	1
Viral Infectious Disorders							
Total patients with at least one AE	0	0	0	5 (<1)	0	5 (<1)	11 (<1)
Herpes zoster	-	-	-	4	-	4	7
Herpes zoster ophthalmic	-	-	-	1	-	1	1
Influenza	-	-	-	-	-	-	1
Varicella	-	-	-	-	-	-	1
Viral infection NOS	-	-	-	-	-	-	1
Opportunistic/Mycobact. Infections							
Total patients with at least one AE	0	0	1 (<1)	0	0	1 (<1)	2 (<1)
Pneumocystis Jiroveci pneumonia	-	-	1	-	-	1	-
Tuberculosis	-	-	-	-	-	-	1
Mycobacterium Avium pneumonia	-	-	-	-	-	-	1

* Includes MTX

Data cut-off April 20, 2007; October 1, 2007 for long-term safety population

Adapted from Table 27 of Module 2.7.4 Summary of Clinical Safety and Table 9 of 120 d safety update

Table 16 Serious Adverse Events

Serious Adverse Events (SAE) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions (>1 Occurrence in Tocilizumab Group***) by Trial Treatment							
	6-months pooled safety population						Long term
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	safety population Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients with ≥ 1 SAE	62 (5)	8 (3)	46 (6)	95 (6)	11 (4)	152 (6)	393 (15)
Total number of SAEs	74	15	51	115	12	178	489
SAEs per 100 pt-yrs	16	12	16	17	10	16	13
Infections and Infestations**	17 (1)	2 (1)	13 (2)	38 (2)	4 (1)	55 (2)	133 (5)
Gastrointestinal Disorders	6 (<1)	1 (<1)	3 (<1)	14 (1)	2 (1)	19 (1)	44 (2)
Abdominal pain	-	-	-	1	-	1	6
Diverticular/Other GI perforation	-	-	-	2	1	3	4
Gastritis/erosive gastritis	-	-	-	1	-	1	3
Inguinal hernia	-	-	-	-	-	-	3
Diarrhea	1	-	-	1	-	1	2
Esophagitis	-	-	1	1	-	2	2
Ischemic colitis/intestinal ischemia	-	-	-	-	-	-	2
Gastric ulcer	-	-	-	1	1	2	1
Pancreatitis	-	-	-	1	-	1	2
Vomiting	1	-	-	1	-	1	2
Injury, Poison., Procedural Complic.***	4 (<1)	3 (1)	4 (<1)	14 (1)	1 (<1)	19 (1)	50 (2)
Neoplasms, benign/malignant/NOS**	4 (<1)	3 (1)	3 (<1)	2 (<1)	1 (<1)	6 (<1)	38 (1)
Musculoskeletal/Connective Tissue***	9 (1)	1 (<1)	3 (<1)	5 (<1)	0	8 (<1)	29 (1)
Cardiac Disorders	5 (<1)	0	1 (<1)	7 (<1)	2 (1)	10 (<1)	22 (1)
Atrial fibrillation	-	-	-	1	-	1	5
Myocardial infarction/AMI	2	-	1	-	-	1	5
Angina/acute coronary synd.	1	-	-	2	-	-	5
Coronary artery disease	-	-	-	2	-	2	2
Arrhythmia	-	-	-	1	-	1	2
Congestive heart failure/LV dysfxn	-	-	-	1	-	1	3
Nervous System Disorders	3 (<1)	0	6 (1)	9 (1)	1 (<1)	16 (1)	17 (1)
Sciatica	-	-	-	1	-	1	4
Cerebrovascular accident	-	-	-	2	-	2	3
Carotid artery stenosis	-	-	1	1	-	2	2
Hemorrhagic stroke	-	-	-	2	-	2	-
Syncope	-	-	2	-	-	2	1
Respiratory/Thoracic/Mediastinal	3 (<1)	1 (<1)	2 (<1)	4 (<1)	0	6 (<1)	15 (1)
Interstitial lung disease/IPF	-	-	2	1	-	3	3
Pulmonary embolism	1	1	-	3	-	3	3
COPD	-	-	-	-	-	-	2
Rheumatoid Lung	-	-	-	-	-	-	2
Vascular Disorders	4 (<1)	1 (<1)	2 (<1)	2 (<1)	0	4 (<1)	15 (1)
Hypertension	-	-	-	1	-	1	3
Deep vein thrombosis	2	-	1	-	-	1	2
Peripheral vascular disorder	-	-	-	-	-	-	2
Renal/Urinary	1 (<1)	0	1 (<1)	3 (<1)	0	4 (<1)	8 (<1)
Nephrolithiasis/ureterolithiasis	-	-	-	2	-	2	6
Hepatobiliary	1 (<1)	0	0	2 (<1)	1 (<1)	3 (<1)	6 (<1)
Cholelithiasis	1	-	-	1	-	1	2
General and Admin site	4 (<1)	1 (<1)	0	2 (<1)	0	2 (<1)	6 (<1)
Non-cardiac chest pain	2	-	-	-	-	-	2
Reproductive/Breast	1 (<1)	0	1 (<1)	1 (<1)	0	2 (<1)	6 (<1)
Uterine hemorrhage	-	-	-	1	-	1	2
Blood and Lymphatic	2 (<1)	0	4 (<1)	2 (<1)	0	6 (<1)	4 (<1)
Leukopenia/neutropenia	-	-	2	2	-	4	4
Psychiatric Disorders	1 (<1)	1 (<1)	2 (<1)	1 (<1)	-	3 (<1)	4 (<1)
Skin and Subcutaneous	1 (<1)	0	0	2 (<1)	0	2 (<1)	2 (<1)
Immune System	0	0	2 (<1)	0	0	2 (<1)	-
Anaphylactic reaction	-	-	2	-	-	2	-
Metabolism/Nutrition	2 (<1)	0	1 (<1)	0	0	1 (<1)	-
Surgical/Medical Procedures	0	0	1 (<1)	1 (<1)	0	2 (<1)	-
Abortion, induced	-	-	1	1	-	2	-
Ear and Labyrinth	2 (<1)	0	0	0	0	0	2 (<1)
Endocrine	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Investigations	0	0	0	1 (<1)	0	1 (<1)	-

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

** See separate SIE and Neoplasms tables for details

***Preferred terms not listed for Injury and Musculoskeletal SOCs

Adapted from Table 24 of Module 2.7.4 Summary of Clinical Safety and Table stae11_sl of 120 d safety update

Adverse Events Causing Discontinuation

Table 17 Adverse Events Causing Discontinuation

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, with Selected Preferred Terms							
	6-months pooled safety population						Long term
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	safety population Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients discontinuing due to AE	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discont.	29	15	38	75	11	124	159
Investigations	3 (<1)	4 (1)	15 (2)	37 (2)	2 (1)	54 (2)	40 (2)
ALT or AST increased ^a	2	4	10	21	1	32	22
Neutrophils decreased ^b	-	-	3	6	1	10	8
Bilirubin increased ^c	-	-	2	7	-	9	4
Infections and Infestations	7 (1)	1 (<1)	5 (1)	8 (<1)	1 (<1)	14 (<1)	24 (1)
Pneumonia	2	-	2	1	1	4	7
Cellulitis	-	-	-	2	-	2	3
Neoplasms, benign/malignant/NOS	1 (<1)	3 (1)	1 (<1)	0	1 (<1)	2 (<1)	27 (1)
Lung cancer ^d	-	1	-	-	-	-	7
Breast cancer	-	-	-	-	-	-	3
Gastric cancer	-	-	-	-	1	1	2
Gastrointestinal Disorders	1 (<1)	5 (2)	1 (<1)	11 (1)	1 (<1)	13 (<1)	15 (1)
GI perforation ^e	-	-	-	2	1	3	3
Skin and Subcutaneous Tissue	1 (<1)	0	3 (<1)	6 (<1)	0	9 (<1)	9 (<1)
Respiratory/Thoracic/Mediastinal	1 (<1)	0	1 (<1)	1 (<1)	0	2 (<1)	11 (<1)
Immune System Disorders	0	1 (<1)	3 (<1)	3 (<1)	0	6 (<1)	3 (<1)
Anaphylactic reaction	-	-	2	1	-	3	2
Hypersensitivity	-	-	1	2	-	3	1
Nervous System Disorders	2 (<1)	0	1 (<1)	3 (<1)	1 (<1)	5 (<1)	4 (<1)
Axonal neuropathy	-	-	-	-	-	-	2
Demyelination	-	-	-	-	-	-	1
Cardiac Disorders	1 (<1)	0	0	1 (<1)	1 (<1)	2 (<1)	6 (<1)
Hepatobiliary Disorders	0	0	0	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Vascular Disorders	2 (<1)	0	1 (<1)	0	0	1 (<1)	4 (<1)
Vasculitis ^f	-	-	-	-	-	-	3
Musculoskeletal and Connective Tissue	6 (<1)	0	2 (<1)	0	1 (<1)	3 (<1)	2 (<1)
General Disorders/Admin. Site	3 (<1)	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Infusion related reaction	1	-	-	1	1	2	-
Pregnancy/Puerperium/Perinatal	1 (<1)	0	1 (<1)	0	0	1 (<1)	3 (<1)
Injury/Poison./Procedural Complic.	0	0	1 (<1)	2 (<1)	0	3 (<1)	1 (<1)
Psychiatric Disorders	0	1 (<1)	0	0	0	0	2 (<1)
Renal and Urinary Disorders	0	0	0	0	0	0	2 (<1)
Blood and Lymphatic System Disorders	0	0	1 (<1)	0	0	1 (<1)	0
Metabolism and Nutrition Disorders	0	0	1 (<1)	0	0	1 (<1)	0

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

Multiple occurrences of the same AE in one individual are counted only once

Events on escape therapy are excluded

a) includes preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal

b) includes Blood and Lymphatic System Disorders preferred terms of neutropenia and leukopenia

c) includes Hepatobiliary Disorders preferred term of hyperbilirubinemia

d) includes preferred terms: lung adenocarcinoma, lung adenocarcinoma metastatic, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified, non-small cell lung cancer, small cell lung cancer stage unspecified

e) includes preferred terms: diverticular perforation, gastrointestinal perforation, large intestine perforation

f) includes preferred terms: rheumatoid vasculitis, vasculitis, vasculitis necrotising

Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

The study protocols mandated discontinuation for patients meeting certain laboratory criteria, such as AST/ALT $\geq 3 \times \text{ULN}$ that persisted or recurred upon re-exposure of treatment, AST/ALT $> 5 \times \text{ULN}$, total bilirubin $> 2.5 \text{ mg/dl}$ or unconjugated bilirubin $> 2 \times \text{ULN}$, and ANC $< 0.5 \times 10^9/\text{L}$. As summarized in Table 17, above, these protocol-mandated laboratory discontinuations were the most common reason for discontinuation. Laboratory abnormalities are discussed in further detail below. Infections and malignancies were the next most common types of events causing discontinuation. For a more detailed listing of the preferred terms associated with the adverse events causing discontinuation, refer to Table 33 in the appendix.

Other Adverse Events of Interest
GI Perforations

In the global RA TCZ program, to include the Roche and Chugai studies, as of December 31, 2007, approximately 4700 patients were exposed to TCZ for approximately 7961 patient-years cumulative exposure. A total of 16 GI perforation events occurred in 15 patients [one patient had both an upper GI (UGI) and a lower (LGI) event]. Compared to RA patients in the United Health Care database and the Marketscan database, RA patients in the TCZ global program had a slightly higher incidence of UGI perforation events and a similar incidence of LGI perforation events.

Table 18 Exposure-Adjusted Incidence of GI Perforations

Exposure-Adjusted Incidence of GI Perforations in RA Patients				
	TCZ program Events	TCZ program Events/100 pt-yrs	UHC database Events/100 pt-yrs	Marketscan database Events/100 pt-yrs
Upper GI	4	0.05	0.03	0.02
Lower GI	12	0.15	0.16	0.14
Total	16	0.20	0.18	0.16

Data cut-off December 31, 2007

Sources: Tables 14 and 15 of 120 day safety update

Almost all events occurred while patients were on TCZ 8 mg/kg, however TCZ 8 mg/kg was the default dose for the open-label extensions. The duration of TCZ exposure before event occurrence varied between 1 and 36 months. For additional details of the cases, refer to line listing table 34 in the appendix.

Demyelinating Disorders

Table 19 Demyelinating Adverse Events in the TCZ Global Program

Demyelinating AEs in the Tocilizumab Global Program								
Study	Event	Age/Gender	TCZ dose	Doses prior to event	Latency (months)	Concomitant diagnoses	Outcome	Comments
WA18062/18696	L sided pos Babinski & tremor; MRI c/w white matter lesions & parietal lobe atrophy	64/M	8 mg/kg	11 to 14 (escape at week 16)	14	migraines hypothyroid peripheral vascular dz	tremor dx'd as benign essential tx with topiramate	withdrawn
WA17823	Blurred vision, dx with cataracts and bilateral optic neuritis	73/F	Blinded	8	8	on INH for pos PPD HTN, osteoporosis	No other demyel. lesions on MRI	continued
WA18062/18696	Progressive weakness & wt loss, dx as chronic idiopathic polyradiculoneuropathy	68/F	8 mg/kg	~11	~10	COPD, HTN, HLD DVT, osteoporosis	death	
MRA213JP/ MRA215JP	deteriorating mental status, dx as leukoencephalopathy	72/F	8 mg/kg	50	~50	Type II DM, HTN HLD, aortic stenosis osteoporosis	extensive white matter lesions neg w/u (inc. PML)	withdrawn

Source: BLA 125276 amendment 11 case narratives

Four patients experienced demyelinating neurologic events in the global TCZ program, as detailed in Table 19, above. The background risk of demyelinating disorders in RA patients is not currently known.

Common Adverse Events

Table 20 Common Adverse Events by System-Organ-Class and Trial Treatment

Common Adverse Events in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by System Organ Class and Trial Treatment							
	6-months pooled safety population						Long term
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	safety population Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Patients with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Infections and Infestations	365 (31)	106 (37)	266 (34)	581 (37)	96 (33)	943 (36)	1555 (61)
Gastrointestinal Disorders	191 (16)	89 (31)	164 (21)	342 (22)	86 (30)	592 (22)	1052 (41)
Skin and Subcutaneous	94 (8)	32 (11)	118 (15)	253 (16)	42 (15)	413 (16)	650 (25)
Musculoskeletal/Connective Tissue	173 (15)	32 (11)	98 (13)	187 (12)	33 (11)	318 (12)	793 (31)
Nervous System	104 (9)	18 (6)	90 (12)	193 (12)	37 (13)	320 (12)	561 (22)
Investigations	46 (4)	43 (15)	80 (10)	192 (12)	48 (17)	320 (12)	470 (18)
General/Admin site	91 (8)	24 (8)	74 (10)	133 (8)	21 (7)	228 (9)	386 (15)
Respiratory/Thoracic/Mediastinal	72 (6)	19 (7)	58 (7)	132 (8)	26 (9)	216 (8)	442 (17)
Injury/Poisoning/Procedural Comp.	67 (6)	15 (5)	50 (6)	114 (7)	14 (5)	178 (7)	439 (17)
Vascular	60 (5)	13 (5)	59 (8)	102 (6)	24 (8)	185 (7)	373 (15)
Psychiatric	35 (3)	11 (4)	33 (4)	57 (4)	20 (7)	110 (4)	232 (9)
Eye Disorders	28 (2)	9 (3)	23 (3)	62 (4)	15 (5)	100 (4)	244 (9)
Metabolism/Nutrition	32 (3)	5 (2)	27 (3)	55 (3)	8 (3)	90 (3)	268 (10)
Blood and Lymphatic	26 (2)	9 (3)	18 (2)	62 (4)	11 (4)	91 (3)	196 (8)
Reproductive/Breast	17 (1)	6 (2)	15 (2)	37 (2)	13 (5)	65 (2)	127 (5)
Cardiac	17 (1)	7 (2)	8 (1)	30 (2)	8 (3)	46 (2)	139 (5)
Renal/Urinary	21 (2)	5 (2)	11 (1)	30 (2)	10 (3)	51 (2)	105 (4)
Ear/Labyrinth	21 (2)	3 (1)	17 (2)	23 (1)	3 (1)	43 (2)	103 (4)
Neoplasms, benign/malignant/NOS	9 (1)	4 (1)	13 (2)	22 (1)	3 (1)	38 (1)	117 (5)
Hepatobiliary	4 (<1)	4 (1)	3 (<1)	16 (1)	9 (3)	28 (1)	61 (2)
Immune System Disorders	8 (1)	4 (1)	7 (1)	18 (1)	2 (1)	27 (1)	62 (2)
Surgical/Medical Procedures	5 (<1)	-	6 (1)	9 (<1)	2 (1)	17 (1)	53 (2)
Endocrine	1 (<1)	1 (<1)	3 (<1)	10 (1)	3 (1)	16 (1)	28 (1)
Congenital/Familial/Genetic	1 (<1)	-	3 (<1)	2 (<1)	-	5 (<1)	15 (1)
Pregnancy/Puerperium/Perinatal	2 (<1)	-	-	-	-	-	7 (<1)

*includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

Adapted from Table 50 of WA17822 CSR, Table 47 of WA17823 CSR, Table 61 of WA17824 CSR, Table 60 of WA18062 CSR, Table 52 of WA18063 CSR
and Table stae11_1 of 120 day safety update

Overall, the types and incidence of common adverse events in the TCZ RA pivotal trials and long-term extensions were consistent with the patient population and the immunosuppressive nature of the study treatments. Frequency by system-organ-class and trial treatment is listed in Table 20, above. Infections/infestations were again the most common type of adverse event, followed by GI disorders. Table 21 below lists the common events by preferred term occurring in at least 1% of patients in a TCZ treatment group, where occurrence was greater in a TCZ group than placebo. Most events were typical, such as upper respiratory infections and headache. The possible relationship of TCZ treatment with events of hypertension and laboratory abnormalities is discussed in further detail below.

Table 21 Common Adverse Events by Preferred Term and Trial Treatment

Common Adverse Events $\geq 1\%$ in a TCZ group and greater than placebo) in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Preferred Term and Trial Treatment							
	6-months pooled safety population						Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Patients with any AEs	733 (63)	220 (77)	547 (71)	1134 (72)	230 (80)	1911 (72)	2259 (88)
Upper Respiratory Tract Infection	71 (6)	15 (5)	48 (6)	123 (8)	21 (7)	192 (7)	398 (16)
Headache	40 (3)	7 (2)	45 (6)	84 (5)	21 (7)	150 (6)	252 (10)
Nasopharyngitis	52 (4)	17 (6)	33 (4)	88 (6)	20 (7)	141 (5)	309 (12)
Hypertension	32 (3)	6 (2)	32 (4)	70 (4)	16 (6)	118 (4)	243 (9)
Nausea	44 (4)	34 (12)	33 (4)	63 (4)	18 (6)	114 (4)	186 (7)
Diarrhea	38 (3)	15 (5)	31 (4)	61 (4)	15 (5)	107 (4)	243 (9)
Bronchitis	38 (3)	6 (2)	33 (4)	51 (3)	9 (3)	93 (4)	225 (9)
Rash	15 (1)	4 (1)	30 (4)	52 (3)	7 (2)	89 (3)	142 (6)
ALT Increased	10 (1)	11 (4)	22 (3)	50 (3)	16 (6)	88 (3)	103 (4)
Urinary Tract Infection	39 (3)	13 (5)	17 (2)	53 (3)	12 (4)	82 (3)	208 (8)
Back Pain	28 (2)	3 (1)	16 (2)	52 (3)	7 (2)	75 (3)	173 (7)
Dizziness	20 (2)	4 (1)	15 (2)	49 (3)	9 (3)	73 (3)	115 (4)
Sinusitis	24 (2)	11 (4)	16 (2)	46 (3)	9 (3)	71 (3)	178 (7)
Dyspepsia	23 (2)	12 (4)	17 (2)	41 (3)	10 (3)	68 (3)	155 (6)
Abdominal Pain Upper	18 (2)	6 (2)	21 (3)	39 (2)	5 (2)	65 (2)	124 (5)
Cough	22 (2)	1 (<1)	16 (2)	36 (2)	8 (3)	60 (2)	132 (5)
Transaminases Increased	6 (<1)	13 (5)	13 (2)	37 (2)	3 (1)	53 (2)	74 (3)
Pharyngolaryngeal Pain	13 (1)	3 (1)	15 (2)	27 (2)	7 (2)	49 (2)	92 (4)
Edema, Peripheral	17 (1)	-	10 (1)	33 (2)	5 (2)	48 (2)	99 (4)
Mouth Ulceration	6 (<1)	6 (2)	10 (1)	31 (2)	6 (2)	47 (2)	81 (3)
Gastroenteritis	17 (1)	9 (3)	18 (2)	24 (2)	4 (1)	46 (2)	116 (5)
Abdominal Pain	15 (1)	6 (2)	13 (2)	21 (1)	11 (4)	45 (2)	100 (4)
Pruritis	11 (1)	3 (1)	11 (1)	25 (2)	8 (3)	44 (2)	52 (2)
Gastritis	9 (1)	5 (2)	9 (1)	28 (2)	3 (1)	40 (2)	77 (3)
Insomnia	15 (1)	3 (1)	16 (2)	16 (1)	6 (2)	38 (1)	85 (3)
Hepatic Enzyme Increased	7 (1)	8 (3)	9 (1)	23 (1)	6 (2)	38 (1)	62 (2)
Depression	14 (1)	2 (1)	8 (1)	20 (1)	6 (2)	34 (1)	67 (3)
Alopecia	6 (<1)	8 (3)	6 (1)	16 (1)	6 (2)	28 (1)	64 (2)
Leukopenia	1 (<1)	-	4 (<1)	19 (1)	4 (1)	27 (1)	50 (2)
Anxiety	9 (1)	2 (1)	5 (1)	13 (1)	7 (2)	25 (1)	51 (2)
Gastroenteritis, Viral	7 (1)	4 (1)	7 (1)	12 (1)	5 (2)	24 (1)	53 (2)
Conjunctivitis	6 (<1)	1 (<1)	5 (1)	15 (1)	4 (1)	24 (1)	58 (2)
Neutropenia	-	-	3 (<1)	17 (1)	4 (1)	24 (1)	63 (2)
Rhinitis	6 (<1)	6 (2)	11 (1)	10 (1)	2 (1)	23 (1)	46 (2)
Dyspnea	3 (<1)	1 (<1)	8 (1)	13 (1)	1 (<1)	22 (1)	38 (1)
Weight Increased	2 (<1)	1 (<1)	5 (1)	12 (1)	5 (2)	22 (1)	41 (2)
Stomatitis	3 (<1)	5 (2)	4 (<1)	12 (1)	4 (1)	20 (1)	34 (1)
Cystitis	4 (<1)	2 (1)	9 (1)	9 (1)	2 (1)	20 (1)	49 (2)
Hypercholesterolemia	0	1 (<1)	2 (<1)	17 (1)	1 (<1)	20 (1)	90 (4)
Gastroesophageal Reflux Disease	6 (<1)	6 (2)	5 (1)	13 (1)	1 (<1)	19 (1)	58 (2)
Chest Pain	6 (<1)	3 (1)	6 (1)	8 (<1)	4 (1)	18 (1)	27 (1)
Liver Function Test Abnormal	3 (<1)	4 (1)	7 (1)	9 (1)	2 (1)	18 (1)	29 (1)
Paresthesia	6 (<1)	-	3 (<1)	10 (1)	3 (1)	16 (1)	42 (2)
Dysuria	8 (1)	1 (<1)	3 (<1)	7 (<1)	5 (2)	15 (1)	20 (1)
Musculoskeletal Pain	5 (<1)	1 (<1)	6 (1)	6 (<1)	3 (1)	15 (1)	51 (2)
Epistaxis	1 (<1)	4 (1)	2 (<1)	12 (1)	1 (<1)	15 (1)	24 (1)
Flushing	4 (<1)	1 (<1)	5 (1)	5 (<1)	3 (1)	13 (<1)	14 (1)
AST Increased	1 (<1)	1 (<1)	3 (<1)	5 (<1)	5 (2)	13 (<1)	20 (1)
Hypoesthesia	3 (<1)	1 (<1)	4 (<1)	4 (<1)	3 (1)	11 (<1)	22 (1)
Osteoarthritis	4 (<1)	-	2 (<1)	5 (<1)	4 (1)	11 (<1)	37 (1)
Menorrhagia	3 (<1)	1 (<1)	2 (<1)	5 (<1)	3 (1)	10 (<1)	14 (<1)
Hyperlipidemia	3 (<1)	-	3 (<1)	3 (<1)	4 (1)	10 (<1)	44 (2)
Neutrophil Count Decreased	-	-	2 (<1)	4 (<1)	3 (1)	9 (<1)	18 (1)
Palpitations	6 (<1)	3 (1)	2 (<1)	4 (<1)	2 (1)	8 (<1)	27 (1)
Abdominal Discomfort	2 (<1)	-	2 (<1)	3 (<1)	3 (1)	8 (<1)	23 (1)
Blood Triglycerides Increased	-	-	-	5 (<1)	3 (1)	8 (<1)	24 (1)

*includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

Multiple occurrences of the same adverse event in one individual counted only once.

Events on escape therapy are excluded.

Adapted from Table stae13_1 of Module 2.7.4 and Table stae11_1 of 120 day safety update.

Laboratory Findings

Treatment with TCZ appeared to result in dose-related changes in certain hematology, hepatobiliary and lipid parameters. Mean changes from baseline are summarized in Table 22, below; changes in absolute neutrophil count (ANC) and platelets are illustrated in Figure 1, below. Overall, changes in neutrophil counts and platelets appeared to remain within the normal range and reverted back toward baseline once treatment ended (at Week 24). TCZ treatment resulted in small mean increases in liver enzyme tests and possibly bilirubin. Changes in lipid parameters were also incrementally small; however all lipid parameters, including total cholesterol, HDL, LDL and triglycerides were increased. Changes of greater magnitude are discussed in further detail below.

Table 22 Mean Change from Baseline in Selected Laboratory Parameters at Week 24

Mean Change from Baseline in Selected Laboratory Parameters at Week 24 in the Tocilizumab RA Pivotal Studies							
		6-months pooled safety population					
	normal range	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ
Enrolled		1170	284	774	1582	288	2644
Hematology							
WBC (10 ⁹ /L)	(4.5-11.0)	-0.1	-1.1	-0.8	-1.9	-2.2	-1.7
Neutrophils (10 ⁹ /L)	(1.8-7.7)	-0.1	-1.0	-0.8	-1.9	-2.2	-1.7
Lymphocytes (10 ⁹ /L)	(1.0-4.8)	-0.9	-0.02	-0.03	0.02	0.1	0.01
Platelets (10 ⁹ /L)	(150-350)	-5	-37	-75	-98	-119	-94
Hemoglobin (g/L)	(130-180)	-1	2	6	11	13	10
Hepatobiliary							
AST (U/L)	(0-40)	0	3	3	7	6	6
ALT (U/L)	(0-55)	2	8	9	16	13	14
Total Bilirubin (umol/L)	(0-17)	0	1	2	3	3	3
Alkaline Phosphatase (U/L)	(0-115)	-1	-2	-12	-20	-20	-18
Lipids							
Cholesterol (mmol/L)	(0-6.18)	0.10	0.19	0.42	0.77	0.96	0.70
HDL (mmol/L)	(0.91-n.d.)	0.02	0.08	0.08	0.13	0.11	0.11
LDL (mmol/L)	(0-4.13)	0.05	0.13	0.31	0.52	0.68	0.48
Triglycerides (mmol/L)	(0.45-1.69)	0.02	-0.05	0.09	0.32	0.44	0.27
Total Cholesterol/HDL ratio	(n.d.-5.00)	0.01	-0.09	0.14	0.25	0.46	0.24
LDL/HDL ratio	(n.d.-7.10)	0	-0.03	0.12	0.16	0.31	0.17

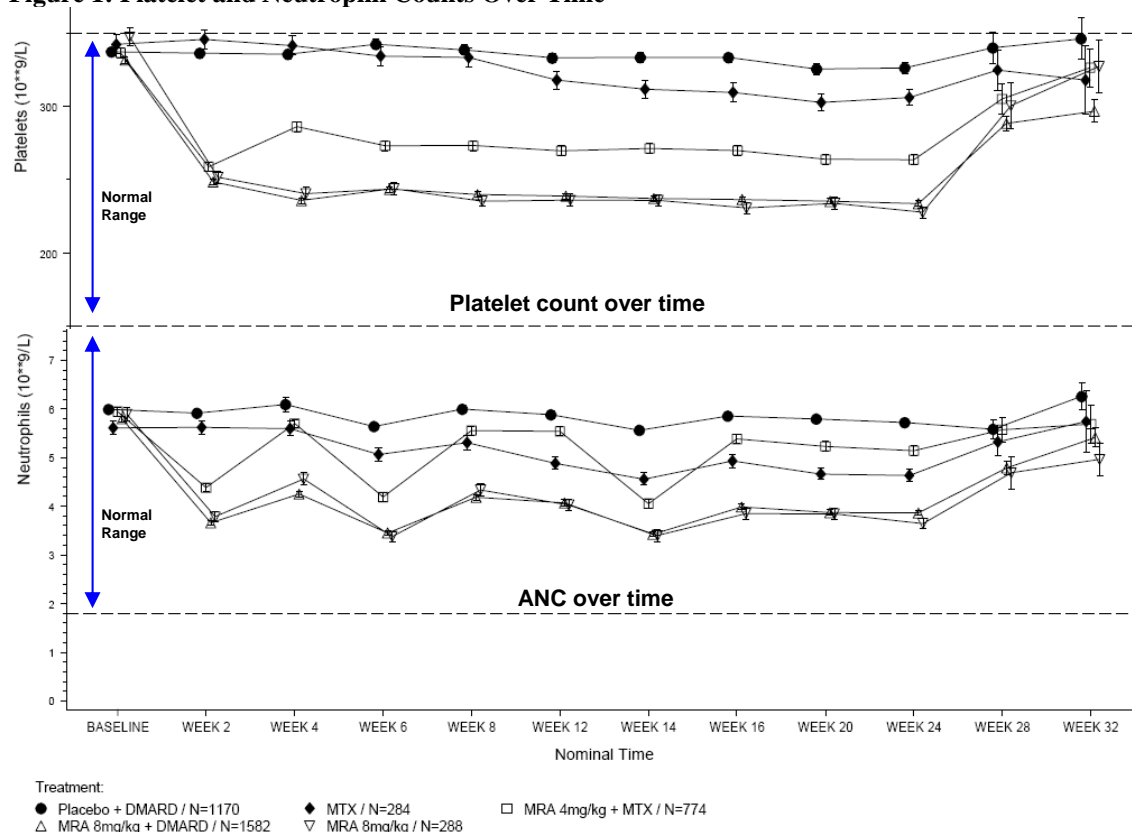
*Includes MTX

Worst values within a time window per patient are summarized

Escape data is excluded

Adapted from Table 41 and Table stlb10_sum of Module 2.7.4

Figure 1: Platelet and Neutrophil Counts Over Time



Only worst values within a time window per patient are summarized. Escape data excluded.
Taken from Figures 2 and 3 of Module 2.7.4 Summary of Clinical Safety

Marked Laboratory Abnormalities

Hematology parameters:

As noted in Table 23 below, few patients reached the protocol-mandated discontinuation point of $ANC \leq 0.5 \times 10^9/L$ during the 6-month controlled period, however those who did were on TCZ treatment. Discontinuation criteria were not pre-specified for other hematology parameters. A higher proportion of TCZ-treated patients met protocol-defined criteria for markedly low WBC or neutrophils, however these low white blood cell counts were not associated with infectious adverse events. Similarly, a higher proportion of TCZ-treated patients met protocol-defined criteria for at least one markedly low platelet count, but few of these patients had replicated values meeting these criteria. Low platelet counts were not associated with bleeding adverse events.

Table 23 Markedly Abnormal Hematology Parameters

Markedly Abnormal Hematology Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
	normal range	markedly abnl def.	Placebo + DMARD*	MTX	6-months pooled safety population			Long term safety population Pooled TCZ
					TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ
Enrolled			1170	284	774	1582	288	2644
Pts discontinued for abnl Dose mod/interrupted			-	-	3 (<1)	7 (<1)	1 (<1)	11 (<1)
WBC (10 ⁹ /L), low	(4.5-11.0)	<3, >18	-	1 (<1)	3 (<1)	9 (1)	7 (2)	19 (1)
single, not last value			9 (<1)	3 (1)	28 (4)	98 (6)	7 (2)	133 (5)
last value or replicated any value			1 (<1)	3 (1)	8 (1)	53 (3)	5 (2)	66 (3)
Neutrophils (10 ⁹ /L), low	(1.8-7.7)	<1.5, >9.25	10 (<1)	6 (2)	36 (5)	151 (10)	12 (4)	199 (8)
single, not last value			9 (<1)	4 (1)	55 (7)	141 (9)	22 (8)	218 (8)
last value or replicated any value			1 (<1)	3 (1)	14 (2)	90 (6)	17 (6)	121 (5)
Lymphocytes (10 ⁹ /L), low	(1.0-4.8)	<0.7, >7.6	10 (<1)	7 (2)	69 (9)	231 (15)	39 (14)	339 (13)
single, not last value			46 (4)	12 (4)	35 (5)	49 (3)	5 (2)	89 (3)
last value or replicated any value			22 (2)	3 (1)	10 (1)	22 (1)	1 (<1)	33 (1)
Platelets (10 ⁹ /L), low	(150-350)	<100, >550	68 (6)	15 (5)	45 (6)	71 (4)	6 (2)	122 (5)
single, not last value			2 (<1)	-	7 (<1)	20 (1)	2 (<1)	29 (1)
last value or replicated any value			4 (<1)	-	3 (<1)	7 (<1)	2 (<1)	12 (<1)
Hemoglobin (g/L), low	(130-180)	<110, >200	6 (<1)	-	10 (1)	27 (2)	4 (1)	41 (2)
single, not last value			29 (2)	15 (5)	5 (<1)	11 (<1)	-	16 (<1)
last value or replicated any value			37 (3)	7 (2)	13 (2)	14 (<1)	1 (<1)	28 (1)
			66 (6)	22 (8)	18 (2)	25 (2)	1 (<1)	44 (2)
								72 (3)

*Includes MTX

Worst values within a time window per patient are summarized

Escape data is excluded

Sources: Table stlb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stlb10_idl_ssta and stlb10_mark of 120 day safety update

Hepatobiliary parameters:

Per protocol, patients experiencing 2 transaminase elevations ≥ 3 X ULN on treatment were permanently discontinued from study drug. Patients experiencing any transaminase elevations > 5 X ULN or total bilirubin > 2.5 mg/dL or unconjugated bilirubin levels > 2 X ULN were also to be permanently discontinued from study drug in the core studies. The number of patients actually discontinued for these reasons was low, but the proportion was higher in the TCZ treatment groups, as summarized in Table 24, below.

Table 24 Markedly Abnormal Hepatobiliary Parameters

Markedly Abnormal Hepatobiliary Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
	normal range	markedly abnl def.	Placebo + DMARD*	MTX	6-months pooled safety population			Long term safety population Pooled TCZ
					TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ
Enrolled			1170	284	774	1582	288	2644
Pts discontinued for abnl Dose mod/interrupted			2 (<1)	4 (1)	12 (2)	28 (2)	1 (<1)	41 (2)
AST (U/L)	(0-40)	>80	8 (1)	24 (8)	19 (2)	37 (2)	22 (8)	78 (3)
single, not last value			10 (<1)	12 (4)	30 (4)	59 (4)	5 (2)	94 (4)
last value or replicated any value			3 (<1)	2 (<1)	7 (<1)	35 (2)	0	42 (2)
ALT (U/L)	(0-55)	>110	13 (1)	14 (5)	37 (5)	94 (6)	5 (2)	136 (5)
single, not last value			39 (3)	22 (8)	67 (9)	139 (9)	16 (6)	222 (8)
last value or replicated any value			16 (1)	11 (4)	34 (4)	123 (8)	12 (4)	169 (6)
Total Bilirubin (umol/L)	(0-17)	>34	55 (5)	33 (12)	101 (13)	262 (17)	28 (10)	391 (15)
single, not last value			1 (<1)	0	2 (<1)	8 (<1)	0	10 (<1)
last value or replicated any value			0	0	2 (<1)	4 (<1)	0	6 (<1)
Alkaline Phosphatase (U/L)	(0-115)	>220	1 (<1)	0	2 (<1)	12 (<1)	0	16 (<1)
single, not last value			6 (<1)	4 (1)	1 (<1)	5 (<1)	1 (<1)	7 (<1)
last value or replicated any value			2 (<1)	2 (<1)	2 (<1)	2 (<1)	0	4 (<1)
			8 (<1)	6 (2)	3 (<1)	7 (<1)	1 (<1)	11 (<1)
								13 (<1)

*Includes MTX

Worst values within a time window per patient are summarized

Escape data is excluded

Sources: Table stlb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stlb10_idl_ssta and stlb10_mark of 120 day safety update

Dose modification or interruption for hepatobiliary laboratory abnormalities was also more frequent in the TCZ treatment groups compared with placebo. Overall, TCZ treatment was associated with a higher incidence of markedly abnormal (as defined by the sponsor) AST/ALT elevation.

No instances of liver enzyme elevations to $>3 \times \text{ULN}$ with concomitant increase in total bilirubin to $>2 \times \text{ULN}$ were noted in the 6-months safety population. One female patient in her late 50's received tocilizumab 8 mg/kg for 6 months in the randomized trial without significant problems but subsequently, in the long-term extension, started concomitant MTX for the first time at 20 mg weekly and had a simultaneous increase in ALT and AST to $>8 \times \text{ULN}$ and total bilirubin to $>2 \times \text{ULN}$ (primarily due to elevations of indirect bilirubin). Alkaline phosphatase levels remained in the normal range during the episode, although one subsequent alkaline phosphatase level was slightly elevated (130 with normal range 35-123 U/L). The patient's MTX dose was lowered and her TCZ was held, however liver enzyme elevations recurred when the patient was re-started on a lower dose of TCZ (4 mg/kg). There were no clinical symptoms associated with these laboratory abnormalities, but the patient was withdrawn due to abnormal liver enzymes. The event subsequently resolved, and ALT, AST, alkaline phosphatase, and bilirubin values returned to their normal range.

Overall, in patients experiencing liver enzyme elevations who continued on study, modification of treatment regimen (a reduction of the dose of DMARD, an interruption of TCZ infusion and/or reduction of TCZ dose from 8 mg/kg to 4 mg/kg) led to a decrease or a normalization without subsequent elevation of liver enzymes, or occurrence of hepatobiliary AEs. Currently available data on over 3700 patients treated with TCZ for up to 2 years show contain no clinical events of hepatitis or hepatic failure.

Lipid parameters

Table 25 Markedly Abnormal Lipid Parameters

Markedly Abnormal Lipid Parameters in the Tocilizumab RA Pivotal Studies and Long-Term Extensions								
	normal range	markedly abnl def.	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	Long term safety population Pooled TCZ
Enrolled			1170	284	774	1582	288	2644
Pts discontinued for abnl			-	-	-	-	-	1 (<1)
Dose mod/interrupted			-	-	-	-	-	5 (<1)
Lipid lowering agent started			13 (1)	2 (1)	15 (2)	19 (1)	3 (1)	180 (7)
Cholesterol (mmol/L)	(0-6.18)	>8.30						
single, not last value			1 (<1)	2 (<1)	14 (2)	30 (2)	11 (4)	103 (4)
last value or replicated			1 (<1)	0	6 (<1)	28 (2)	12 (4)	82 (3)
any value			2 (<1)	2 (<1)	20 (3)	58 (4)	23 (8)	185 (7)
HDL (mmol/L)	(0.91-n.d.)	<0.65						
single, not last value			0	0	0	1 (<1)	2 (<1)	10 (<1)
last value or replicated			1 (<1)	1 (<1)	2 (<1)	1 (<1)	0	5 (<1)
any value			1 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	15 (<1)
LDL (mmol/L)	(0-4.13)	>5.4						
single, not last value			3 (<1)	3 (1)	17 (2)	37 (2)	12 (4)	128 (5)
last value or replicated			3 (<1)	1 (<1)	13 (2)	58 (4)	17 (6)	144 (6)
any value			6 (<1)	4 (1)	30 (4)	95 (6)	29 (11)	272 (11)
Triglycerides (mmol/L)	(0.45-1.69)	>2.83						
single, not last value			7 (<1)	1 (<1)	38 (5)	77 (5)	20 (7)	245 (10)
last value or replicated			9 (<1)	0	23 (3)	77 (5)	19 (7)	185 (7)
any value			16 (1)	1 (<1)	61 (8)	154 (10)	39 (14)	430 (17)

*Includes MTX

Worst values within a time window per patient are summarized

Escape data is excluded

Sources: Table stlb10_mark of Module 2.7.4, Pg. 94 and Tables stae11_wd, stae11_dmod, stlb10_idl_ssta and stlb10_mark of 120 day safety update

As shown above in Table 25, very few patients experienced markedly low HDLs, however a higher proportion of patients in the TCZ treatment groups met sponsor-defined criteria for markedly abnormal elevations in total cholesterol, LDL, and triglycerides. Lipid-lowering agents could be initiated at the discretion of patients' health care providers but were not mandated in the study protocols. The proportion of patients started on lipid-lowering agents in the RA pivotal trials/extensions (1-2% in the controlled period, 7% in the long-term extensions) does not appear to be excessive, given the underlying cardiovascular risk and co-morbidities in the RA patient population. Cardiovascular events have been discussed above in the serious adverse events section; thus far, MI and CVA rates in the RA pivotal studies/extensions are not elevated compared to rates described in the literature.

Vital Signs

A higher proportion of patients in the TCZ treatment groups experienced elevations of 20 mmHg or more in systolic and/or diastolic blood pressure, summarized in Table 26, below. Blood pressure elevation was transient, and no permanent changes were noted, as evidenced by lack of change in baseline vs. last post-baseline mean blood pressures. The few HTN-related SAEs reported during the 6-month controlled period occurred in the TCZ 8 mg/kg + DMARD treatment arm; however, as previously noted, exposure-adjusted rates of stroke events overall are within expected rates for the RA patient population.

Table 26 Effect of TCZ on Blood Pressure

Effect of Tocilizumab on Blood Pressure (6 Month Pooled Safety Population) by Trial Treatment					
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg
Enrolled	1170	284	774	1582	288
Highest BP reading (mmHg)	n (%)	n (%)	n (%)	n (%)	n (%)
Systolic BP					
>150 and ↑ by >10 to ≤20	109 (9)	24 (8)	49 (6)	150 (9)	30 (10)
>150 and ↑ by >20	137 (12)	30 (11)	94 (12)	238 (15)	43 (15)
Diastolic BP					
>90 and ↑ by >10 to ≤20	125 (11)	31 (11)	93 (12)	235 (15)	40 (14)
>90 and ↑ by >20	73 (6)	10 (4)	62 (8)	129 (8)	29 (10)
HTN-related AEs reported	n (%)	n (%)	n (%)	n (%)	n (%)
Infusion-related hypertension	10 (1)	2 (1)	7 (1)	17 (1)	7 (2)
Hypertension NOS	32 (3)	6 (2)	32 (4)	70 (4)	16 (6)
SAE, Hypertension	-	-	-	1 (<1)	-
SAE, CVA	-	-	-	2 (<1)	-
SAE, Hemorrhagic stroke	-	-	-	2 (<1)	-
Baseline vs. Post-Baseline					
Systolic BP*					
Baseline mean	125	125	124	125	126
Post-baseline mean**	124	123	123	125	126
Diastolic BP*					
Baseline mean	76	77	76	76	77
Post-baseline mean**	76	76	76	77	78

* Blood pressure taken semi-supine (mmHg)

** Post baseline values are last post-baseline observation per patient

Escape data are excluded

Adapted from Tables 24, 50, 51, stae11_ir, and stae11-1 of Module 2.7.4

Immunogenicity and Infusion Reactions

Routine samples for anti-TCZ antibody testing were collected at baseline and at months 1, 2, 3, and 6 in the pivotal studies, and every 24 weeks in the long-term extensions. In addition to routine testing, patients who experienced an adverse event of “potential immunogenic nature” (defined in the study protocol) or patients who discontinued treatment because of insufficient therapeutic response underwent immunogenicity testing. These results are summarized in Table 27, below.

A very small proportion of patients tested returned positive for anti-TCZ antibodies (46/2553, 1.8%) in the TCZ treatment groups of the 6-month safety population. Approximately 6% (10/159) of patients tested for events of potentially immunogenic origin were positive for anti-TCZ antibodies. Five of these patients had events that resulted in withdrawal, to include anaphylactic reaction, infusion reactions, and hypersensitivity. During the 6-month controlled period, fourteen TCZ-treated patients withdrew for reasons ascribed to insufficient therapeutic response and underwent loss of efficacy (LoE) testing; none of these patients were positive for anti-TCZ antibodies. Subsequently, an additional 50 patients have withdrawn for LoE from the long-term extensions; only one of these patients was positive for anti-TCZ antibodies.

Table 27 Summary of Immunogenicity Testing Results

Summary of Immunogenicity Testing Results							
	6 month pooled safety population						Long term safety population Pooled TCZ ^c
	Placebo + DMARD	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD	TCZ 8mg/kg	All TCZ	
Safety Population	1170	284	774	1582	288	2644	2439
Tested in Screening Assay	611	273	765	1513	275	2553	477
Tested after Escape	235	8	122	95	6	323/546 ^b	n/a
Positive Screening/Confirmation Assays ^c	6 (4 escape)	1	17	23	2	46 (4 escape)	13
Positive neutralizing antibody	2 (all escape)	0	8	19	1	30 (2 escape)	8
Number of patients with event-driven testing	47	8	59	83	17	159	75
Pts with event-driven testing who tested pos.	1 (escape)	0	4	4	1	10 (1 escape)	2
positive screening/confirmation	1 (escape)	0	4	3	1	9 (1 escape)	2
positive neutralizing	0	0	4	4	1	9	1
Ab-pos. pts with events causing withdrawal	1 (escape)	0	2	1	1	5 (1 escape)	0
positive screening/confirmation	1 (escape)	0	2	1	1	5 (1 escape)	0
positive neutralizing	0	0	2	1	1	4	0
No. of Pts with Loss of Efficacy (LoE) testing	28 (1 escape)	3	7	5	1	14 (1 escape)	50
Ab-pos. pts withdrawing due to LoE	0	0	0	0	0	0	1
positive screening/confirmation	0	0	0	0	0	0	1
positive neutralizing	0	0	0	0	0	0	1

a) Only those patients who were not previously tested in the double-blind period are reported

b) includes 323 patients were tested after escaping from placebo/control to TCZ out of 546 total patients who escaped; includes 80 patients from placebo-controlled substudy of WA17824

c) Repeatedly positive or at last testing on study; only post-baseline positive results are counted

Source: BLA 125276 Amendment 18

Table 28 Summary of Infusion Reactions

Infusion Reactions in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Trial Treatment							
	6-months pooled safety population						Long term safety population Pooled TCZ
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	
Enrolled	1170	284	774	1582	288	2644	2562
Pts with ≥1 Infusional AE**	60 (5)	13 (5)	59 (8)	109 (7)	25 (9)	193 (7)	274 (11)
Infusional DAEs	1 (<1)	-	3 (<1)	4 (<1)	1 (<1)	8 (<1)	2 (<1)
Selected AEs Occurring within 24 hours of Infusion:							
Hypertension	10 (1)	2 (1)	7 (1)	17 (1)	7 (2)	31 (1)	61 (2)
Hypotension	6 (1)	1 (<1)	3 (<1)	3 (<1)	1 (<1)	7 (<1)	15 (1)
Rash	3 (<1)	-	9 (1)	12 (1)	2 (1)	22 (1)	26 (1)
Urticaria	-	-	2 (<1)	2 (<1)	-	4 (<1)	7 (<1)
Angioedema	-	-	-	-	-	-	1 (<1)
Anaphylaxis	-	-	3 (<1)	3 (<1)	-	6 (<1)	2 (<1)
Hypersensitivity	-	-	1 (<1)	2 (<1)	-	3 (<1)	-
Infusion related reaction	-	-	2 (<1)	4 (<1)	1 (<1)	7 (<1)	7 (<1)

*Includes MTX

**Includes terms defined in Slae_gloss_ir of 120 day safety update

Sources: BLA Amendment 18 and rhstae11_ir and stae11_ir of 120 day safety update

As shown in Table 27, a small percentage (6%) of patients experiencing adverse events of potentially immunogenic origin tested positive for anti-TCZ antibodies. The majority of patients experiencing acute infusion reactions (Table 28, above) were therefore negative. A higher proportion (7-9% vs. 5% in the placebo or MTX groups) of patients in the TCZ treatment groups experienced acute (within 24 hours) infusional adverse events, and the proportion did increase during the long-term extensions. However, the majority of these patients were able to continue treatment and did not experience recurrence. Of note, a total of 6 patients experienced anaphylactic reactions, all of which resulted in withdrawal; 3 were positive for anti-TCZ antibodies, 1 was negative, and 2

were not tested. Anaphylactic reactions tended to occur after the second to fourth infusions.

Overall, immunogenicity and acute infusion adverse events occurred in a small fraction of patients who received TCZ treatment and did not appear to significantly impact the overall efficacy or safety profile of TCZ treatment. The frequency and severity of these events appear to be consistent with those observed with currently approved biologic treatments for RA.

Conclusion

Table 29 below describes an estimate of the potential benefit vs. potential risks of TCZ treatment in RA. Number-needed-to-treat/-harm (NNT/NNH) calculations were based on the 4 placebo-controlled studies (WA17824 is a non-inferiority study of TCZ 8 mg/kg monotherapy vs. MTX monotherapy), utilizing the comparison of TCZ 8 mg/kg + DMARD vs. placebo + DMARD from the 6-month controlled period.

During this period, the frequency of malignancy diagnoses and lipid-lowering agent starts were the same in the TCZ 8 mg/kg + DMARD group as for the placebo + DMARD group, resulting in an NNH of ∞ . As a caveat, it should be noted that the proportion of patients experiencing malignancy, SAE, SIE or needing to start lipid lowering agents all increased over the duration of the long-term extension studies. However, exposure-adjusted incidence of malignancies remained similar to the controlled period, and exposure-adjusted incidence of serious infections were lower (see Table 11, above). Liver enzyme abnormalities were relatively common. In most cases, liver enzyme elevations were mild to moderate. However, in one patient receiving tocilizumab severe elevations occurred following addition of MTX to levels that met criteria for Hy's law, i.e., ALT and AST levels greater than 3x ULN (upper limit of normal) accompanied by elevated total bilirubin above 2x ULN without evidence of cholestasis. Drugs exhibiting cases of Hy's law have been used at the Food and Drug Administration to identify drugs likely to cause severe liver injury. Of note, the patient in question had MTX added at a dose higher than the usual dose for initiating therapy, i.e., 20 mg/wk. IL6 receptor expression is high in the liver, providing a biologically plausible mechanism for this finding. The rate of GI perforations may be slightly elevated over background rates in RA (see Table 18, above), however were still an uncommon occurrence.

Table 29 Risk-Benefit Overview

Risk-Benefit Overview		
Clinical Activity	Proportion Responding	Number Needed to Treat
ACR20	58%	~3
ACR50	36%	~4
ACR70	18%	~7
Risks	Frequency	Number Needed to Harm
Serious Infection	5.7 per 100 pt-yrs	~56
Malignancy	1.5 per 100 pt-yrs	∞
GI Perforations	0.2 per 100 pt-yrs	~385
Demyelinating AE	.05 per 100 pt-yrs	n.d. ^a
Liver enzyme abnormalities ^b	18 per 100 pt-yrs	~7
Lipid lowering agent starts	2.8 per 100 pt-yrs	∞

Data presented pertains to TCZ 8 mg/kg + DMARD group

NNT/NNH calculations based on comparison with placebo + DMARD, controlled period, exposure adjusted

a) not determinable-one event occurred during a placebo-controlled period, but tx remains blinded

b) based on most common "marked abnormality" of elevated ALT; no clinical hepatotoxicity events noted

Based on the results of the 5 controlled RA trials submitted by the sponsor, treatment with tocilizumab appears to be effective for patients with moderate to severely active RA.

The safety data from these trials, long-term extensions, and the global experience with TCZ overall depict the profile of an immunosuppressant and its inherent risks, such as serious infections. As a monoclonal antibody for infusion, TCZ appears to exhibit an immunogenicity and infusion-reaction profile that is consistent with approved agents of similar design and route of administration. As an IL6 inhibitor, TCZ manifested effects on WBC, liver enzymes, and lipids, although these were not associated with clinical adverse events in the controlled setting of the clinical trial experience. The clinical trial experience has been extensive, but may not capture the full extent of safety concerns that may arise with long-term IL6 inhibition.

The Agency is asking the Committee to review the safety and efficacy data for TCZ and to provide your assessment of the risks and benefits of TCZ treatment, and your judgment as to whether it should be approved for the treatment of moderately to severely active RA.

References

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Appendices

Efficacy

Table 30 Summary of Change in ACR Components and DAS28 from Baseline to Week 24

Summary of Change in ACR Components and DAS28, baseline to Week 24, by Trial and Treatment													
RA Population:	DMARD inadequate			DMARD inadequate			Early RA		TNF inadequate			DMARD inadeq.	
	WA17822	WA17823	WA17824	WA18062	WA18063								
	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	MTX n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 4 n (%)	TCZ 8 n (%)	Pbo n (%)	TCZ 8 n (%)
ITT Population (PP for WA17824)	204	213	205	393	399	398	259	265	158	161	170	413	803
SJC (66 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-4.3	-8.5	-10.5	-2.5	-7.4	-8.5	-7.8	-11.7	-0.5	-6.8	-7.8	-4.9	-10.3
Adjusted Mean Diff.	-	-4.2	-6.2	-	-4.8	-5.9	-	-3.9	-	-6.2	-7.2	-	-5.5
95% CI of Difference	-	(-6.1,-2.3)	(-8.1,-4.2)	-	(-6.1,-3.5)	(-7.2,-4.6)	-	(-5.7,-2.0)	-	(-9.0,-3.5)	(-9.9,-4.5)	-	(-6.7,-4.3)
TJC (68 joints)	n = 204	n = 211	n = 205	n = 391	n = 399	n = 397	n = 256	n = 264	n = 157	n = 160	n = 170	n = 411	n = 801
Adjusted Mean*	-7.4	-14.5	-17.1	-4.9	-12.1	-14.0	-13.5	-17.1	0.3	-10.5	-14.8	-8.5	-15.7
Adjusted Mean Diff.	-	-7.0	-9.6	-	-7.2	-9.1	-	-3.6	-	-10.8	-15.1	-	-7.1
95% CI of Difference	-	(-10.0,-4.1)	(-12.6,-6.7)	-	(-9.2,-5.2)	(-11.1,-7.1)	-	(-6.3,-1.0)	-	(-14.6,-7.1)	(-18.8,-11.4)	-	(-8.9,-5.4)
Patient Global (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 316	n = 230	n = 242	n = 61	n = 106	n = 129	n = 322	n = 729
Adjusted Mean*	-17.8	-28.8	-32.7	-18.4	-24.9	-25.7	-29.5	-33.5	-15.4	-25.4	-32.8	-16.3	-33.2
Adjusted Mean Diff.	-	-10.9	-14.9	-	-6.5	-7.3	-	-4.1	-	-10.0	-17.4	-	-16.8
95% CI of Difference	-	(-17.1,-4.8)	(-20.9,-8.9)	-	(-11.4,-1.6)	(-12.1,-2.4)	-	(-9.3,+1.2)	-	(-20.3,+0.3)	(-27.8,-7.0)	-	(-20.5,-13.2)
Physician Global (mm)	n = 123	n = 158	n = 173	n = 214	n = 307	n = 320	n = 229	n = 242	n = 61	n = 105	n = 127	n = 322	n = 733
Adjusted Mean*	-32.7	-38.3	-41.6	-28.2	-34.0	-38.3	-31.5	-41.6	-20.0	-30.5	-38.2	-21.6	-35.9
Adjusted Mean Diff.	-	-5.6	-9.0	-	-5.8	-10.1	-	-10.1	-	-10.5	-18.2	-	-14.4
95% CI of Difference	-	(-10.5,-0.8)	(-13.8,-4.2)	-	(-9.6,-1.9)	(-14.0,-6.2)	-	(-14.2,-6.0)	-	(-18.6,-2.5)	(-26.3,-10.0)	-	(-17.3,-11.4)
Patient's Pain (mm)	n = 123	n = 156	n = 173	n = 213	n = 308	n = 317	n = 231	n = 242	n = 61	n = 105	n = 129	n = 322	n = 730
Adjusted Mean*	-14.0	-25.0	-29.8	-13.1	-19.3	-22.2	-29.5	-31.5	-8.6	-21.0	-32.5	-12.8	-29.9
Adjusted Mean Diff.	-	-11.0	-15.8	-	-6.2	-9.1	-	-2.0	-	-12.4	-23.9	-	-17.1
95% CI of Difference	-	(-17.0,-5.0)	(-21.7,-9.9)	-	(-10.9,-1.5)	(-13.9,-4.4)	-	(-7.1,+3.1)	-	(-22.1,-2.6)	(-33.7,-14.1)	-	(-20.8,-13.4)
CRP (mg/dL)	n = 122	n = 157	n = 172	n = 214	n = 308	n = 321	n = 230	n = 242	n = 63	n = 106	n = 129	n = 324	n = 727
Adjusted Mean*	-0.35	-1.66	-2.51	-0.14	-0.70	-1.89	-1.81	-2.85	-0.06	-1.40	-2.58	-0.27	-2.19
Adjusted Mean Diff.	-	-1.30	-2.16	-	-0.57	-1.76	-	-1.04	-	-1.34	-2.52	-	-1.93
95% CI of Difference	-	(-2.01,-0.59)	(-2.86,-1.46)	-	(-1.00,-0.13)	(-2.19,-1.32)	-	(-1.67,-0.41)	-	(-2.54,-0.15)	(-3.72,-1.32)	-	(-2.32,-1.54)
ESR (mm/hr)	n = 122	n = 157	n = 174	n = 211	n = 304	n = 318	n = 229	n = 240	n = 62	n = 107	n = 129	n = 325	n = 732
Adjusted Mean*	-7.1	-25.5	-39.5	-7.1	-19.4	-34.6	-15.1	-37.2	-3.0	-19.7	-37.2	-4.7	-35.6
Adjusted Mean Diff.	-	-18.3	-32.3	-	-12.3	-27.5	-	-22.1	-	-16.7	-34.2	-	-30.9
95% CI of Difference	-	(-24.3,-12.4)	(-38.2,-26.5)	-	(-16.7,-8.0)	(-31.9,-23.2)	-	(-27.2,-17.1)	-	(-25.4,-8.1)	(-43.0,-25.5)	-	(-34.2,-27.6)
HAQ-DI	n = 101	n = 126	n = 141	n = 197	n = 292	n = 301	n = 230	n = 243	n = 62	n = 106	n = 130	n = 322	n = 724
Adjusted Mean*	-0.34	-0.52	-0.55	-0.30	-0.41	-0.50	-0.48	-0.70	-0.05	-0.31	-0.39	-0.20	-0.47
Adjusted Mean Diff.	-	-0.18	-0.21	-	-0.10	-0.19	-	-0.22	-	-0.25	-0.34	-	-0.27
95% CI of Difference	-	(-0.34,-0.02)	(-0.37,-0.05)	-	(-0.20,-0.00)	(-0.30,-0.09)	-	(-0.22,-0.34)	-	(-0.42,-0.09)	(-0.51,-0.17)	-	(-0.34,-0.20)
DAS28	n = 121	n = 154	n = 171	n = 208	n = 301	n = 311	n = 227	n = 235	n = 60	n = 104	n = 123	n = 320	n = 710
Adjusted Mean*	-1.55	-2.68	-3.43	-1.45	-2.27	-3.11	-1.99	-3.29	-0.95	-2.04	-3.16	-1.16	-3.17
Adjusted Mean Diff.	-	-1.13	-1.88	-	-0.81	-1.66	-	-1.30	-	-1.09	-2.21	-	-2.01
95% CI of Difference	-	(-1.47,-0.79)	(-2.21,-1.55)	-	(-1.06,-0.57)	(-1.90,-1.42)	-	(-1.58,-1.03)	-	(-1.60,-0.59)	(-2.73,-1.69)	-	(-2.20,-1.82)

*ANOVA

LOCF used for tender and swollen joint counts if missing or patient entered escape

No imputation used for missing HAQ score, CRP, ESR, and VAS assessments

Adapted from Tables 23 and 29 of WA17822 CSR, Tables 22 and 27 of WA17823 CSR, Tables 32 and 38 of WA17824 CSR, Tables 33 and 38 of WA18062 CSR, and Tables 25 and 30 of WA18063 CSR

Percentage improvement in Disease Activity, ACRn, at Week 24

Analyses by Joan Buenconsejo, Ph.D., FDA

X axis = Percentage improvement in disease activity, ACRn, scale 0-100

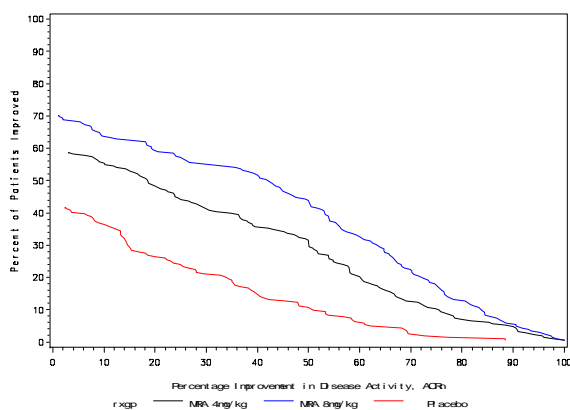
Y axis = Percent of patients improved, scale 0-100

WA17822, 17823, 18062: Blue line = TCZ 8 mg/kg, Black line = TCZ 4 mg/kg, Red line = Placebo

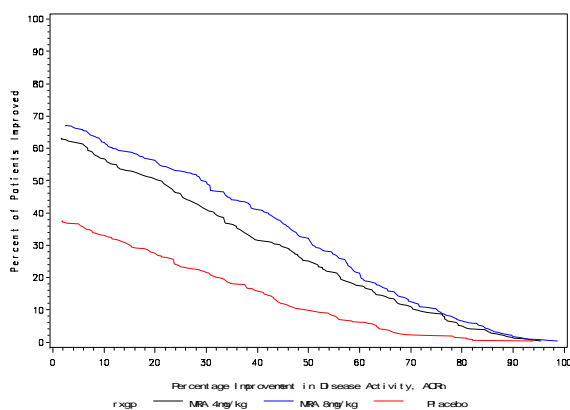
WA18063: Black line = TCZ 8 mg/kg, Red line = Placebo

WA17824: Black line = TCZ 8 mg/kg, Red line = MTX

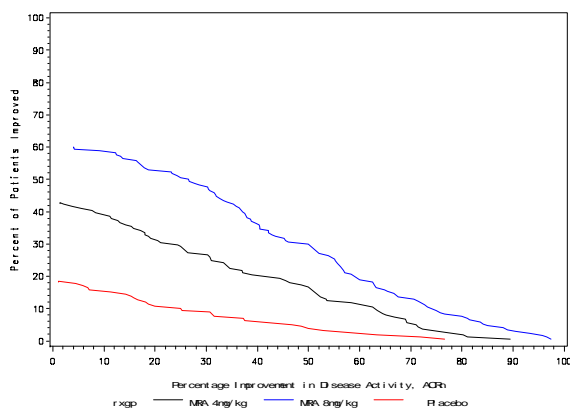
Study WA17822



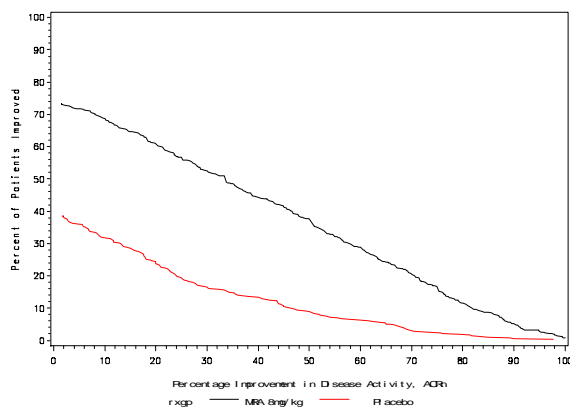
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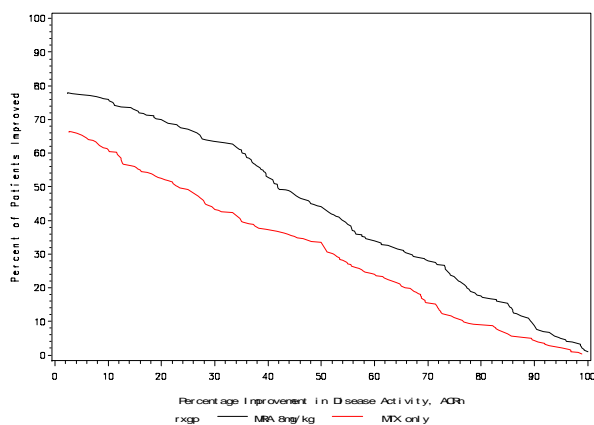
Study WA18062



Study WA18063



Study WA17824



Proportion of ACR Responders by Week

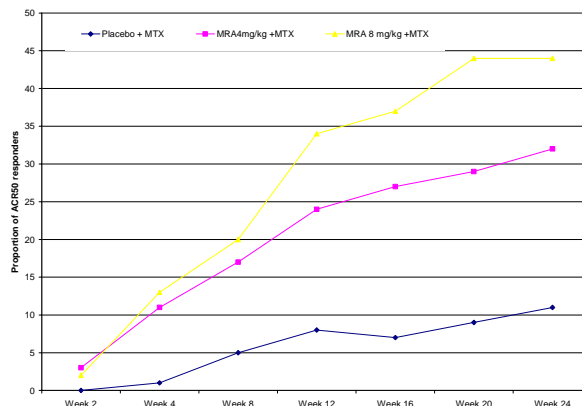
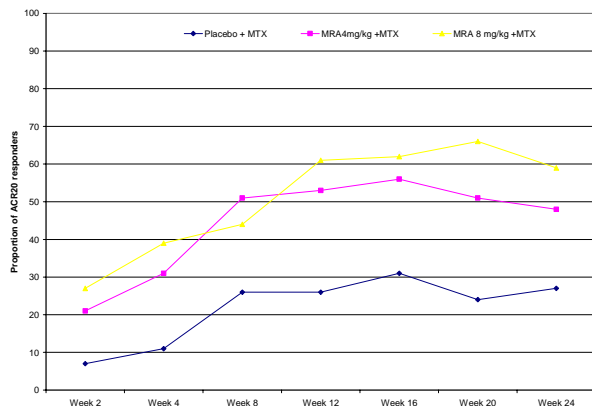
Analyses by Joan Buenconsejo, Ph.D., FDA

Left hand column: ACR 20 responders, scale 0-100

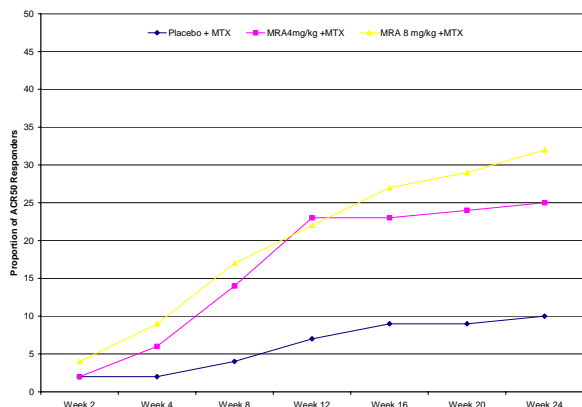
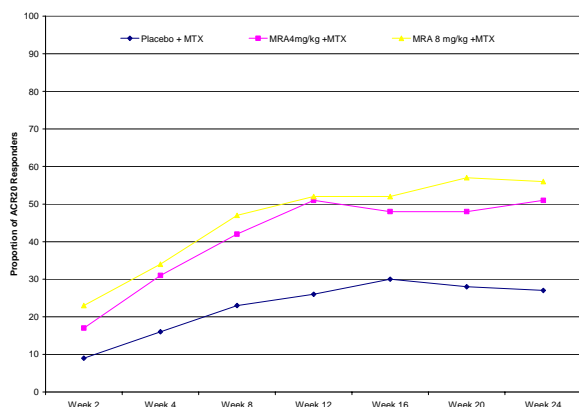
Right hand column: ACR 50 responders, scale 0-50

Yellow line = TCZ 8 mg/kg, Pink line = TCZ 4 mg/kg, Blue line = Placebo

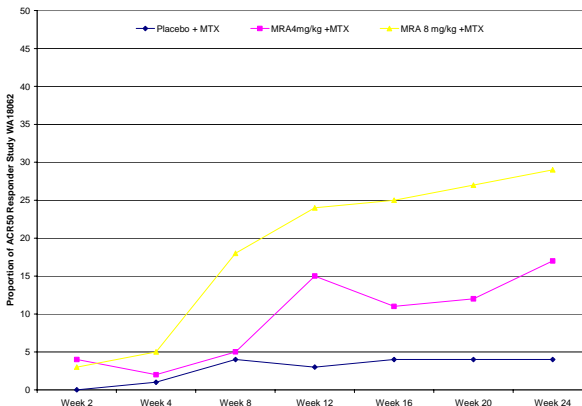
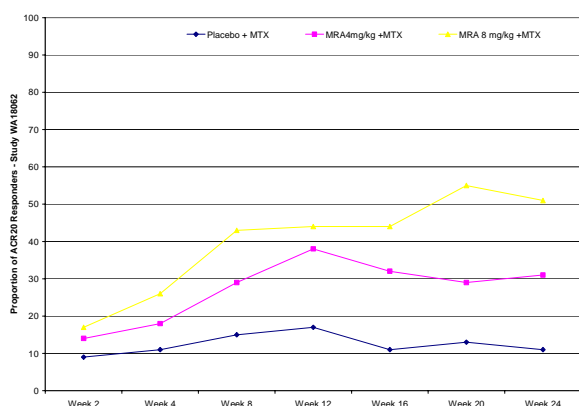
WA17822



WA17823



WA18062



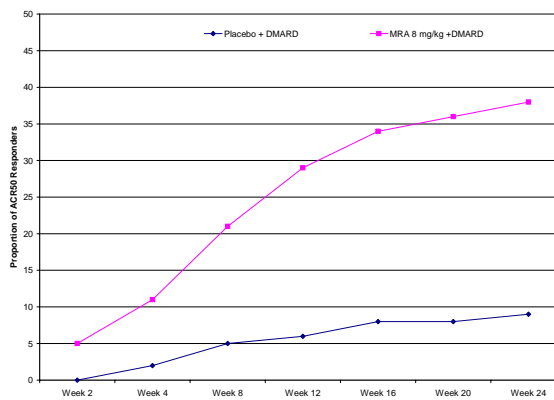
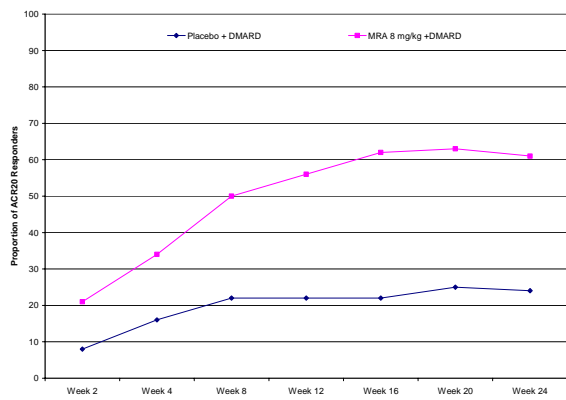
Proportion of ACR Responders by Week (continued)

Left hand column: ACR 20 responders, scale 0-100

Right hand column: ACR 50 responders, scale 0-50

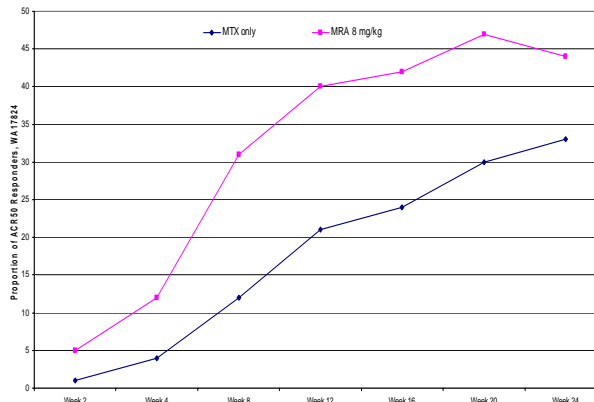
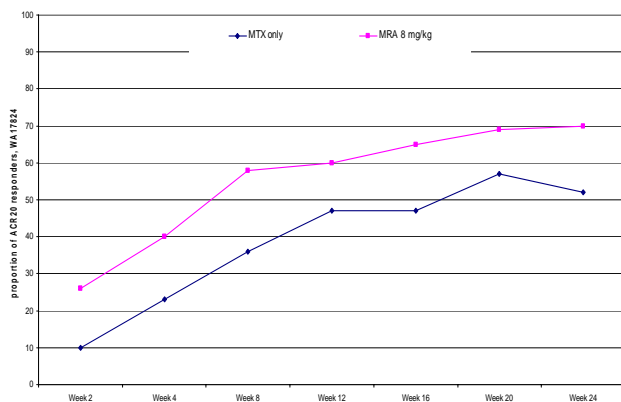
Pink line = TCZ 8 mg/kg, Blue line = Placebo

WA18063



WA17824

Pink line = TCZ 8 mg/kg, Blue line = MTX



Safety Appendices

Table 31 Description of Clinical Studies Contributing Supportive Safety Information

Description of Clinical Studies Contributing Supportive Safety Information							
Study no.	Population	Study Design	Location	Doses/Duration	Safety population		
					total no.	Sex (M/F)	Age (yrs)
Clinical Pharmacology Studies in Healthy Volunteers							
BP19461	Healthy	RDBPCT	UK	TCZ 2,10,20,28 mg/kg SAD, IV	36	19/17	18-61
MRA001JP	Healthy	RSBPCT	Japan	TCZ 0.15,0.5,1, 2 mg/kg SAD, IV	28	28/0	20-29
MRA004JP	Healthy	Open-label	Japan	TCZ 2 mg/kg SAD, IV	6	6/0	20-23
Clinical Pharmacology Studies in RA Patients							
LRO300	DMARD IR	RDBPCT	UK	TCZ 0.1,1,5,10 mg/kg SAD, IV	45	15/30	36-76
MRA002JP	DMARD IR	Open-label	Japan	TCZ 2,4,8 mg/kg, IV q2wks for 24 wks	15	4/11	32-72
MRA220JP	General RA	Open-label	Japan	TCZ 8 mg/kg SAD, IV	31	6/25	23-69
MRA221JP	RA with renal impairment	Open-label	Japan	TCZ 8 mg/kg SAD, IV	14	3/11	56-74
Dose Finding Studies in RA from Chugai Development Program							
LRO301	MTX IR	RDBPCT	Europe	TCZ 2,4 or 8 mg/kg IV w/wo MTX vs. PBO/MTX q4wks for 12 wks	359	77/282	18-76
LRO301A	MTX IR	follow-up	Poland	add'l 16 wk f/u no add'l dosing	86	10/76	22-73
LRO301B	MTX IR w/LFT elevations	follow up	Europe	f/u to LFT outcome no add'l dosing	21	NA	NA
MRA009JP	DMARD IR	RDBPCT	Japan	PBO, TCZ 4 or 8 mg/kg IV q4wks for 8 wks	163	37/126	21-74
Phase 3 Studies in RA from Chugai Development Program							
MRA012JP	DMARD IR	R/open-label	Japan	TCZ 8mg/kg IV q4wks for 52 wks	302	58/244	22-80
MRA213JP	MTX IR	RDBPCT	Japan	TCZ 8 mg/kg or PBO IV q4wks for 24 wks	125	22/103	26-75
Extension Studies in RA from Chugai Development Program (Ongoing)							
MRA010JP	from MRA009JP	Open-label	Japan	TCZ 8mg/kg IV q4wks w/dose adj up to q2wks	144	34/110	21-74
MRA003JP	from MRA002JP	Open-label	Japan	TCZ 2,4,or 8 mg/kg IV q2wks	15	4/11	32-72
MRA214JP	from MRA012JP	Open-label	Japan	TCZ 8mg/kg IV q4wks w/dose adj up to q2wks	241	42/199	23-80
MRA215JP	from MRA213JP	Open-label	Japan	TCZ 8mg/kg IV q4wks w/dose adj up to q2wks	115	20/95	26-76
MRA222JP	from MRA220JP and MRA221JP	Open-label	Japan	no add'l dosing	42	9/33	23-74

Adapted from Sponsor Table 3 of Module 2.7.4 Summary of Clinical Safety
IR = inadequate response

Table 32 Deaths in TCZ-Treated Patients in the Global Safety Database

Line Listing of Deaths in Tocilizumab-Treated Patients in the Global Safety Database			
Indication	Study	Age/Gender	Cause of death
RA	LRO300	70/F	Myocardial ischemia
	LRO301	61/M	Lung cancer
	MRA009JP	60/F	EBV reactivation/Hodgkin's lymphoma
	MRA214JP	52/M	Gastric cancer/pneumonia
	MRA214JP	81/M	Bronchopulmonary aspergillosis
Systemic JIA	Compassionate	5/F	Acute myeloid leukemia
	Compassionate	4/F	Juvenile arthritis
	MRA324JP	4F	Macrophage activation syndrome
	MRA324JP	22/M	Cardiac amyloidosis
Multiple Myeloma	LRO310	57/F	Pneumonia/cholecystitis/neuro symptoms
	LRO310	67/F	Sepsis
	LRO310	77/F	Multiple myeloma
	LRO310	65/F	Multiple myeloma
	LRO310	71/F	Acute renal failure
	Compassionate	53/M	Multiple myeloma
Castleman's Disease	MRA006JP	66/M	Chronic myelomonocytic leukemia
	ML19367	77/F	Cholestatic jaundice
	ML19367	74/F	Gastrointestinal hemorrhage
	ML19367	72/M	Gastric cancer
	ML19367	34/M	Cerebral hemorrhage
	ML19367	46/M	Acute renal failure
	ML19367	38/F	Respiratory failure/Castleman's disease

Data cut-off April 20, 2007

Adapted from Tables 21 and 22 of Module 2.7.4

Table 33 Adverse Events Causing Discontinuation, Unabridged Version

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, Part 1 of 3							
	6-months pooled safety population						Long term
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	safety population Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients discontinuing due to AE	28 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discont.	29	15	38	75	11	124	159
Investigations							
Total patients with at least one AE	3 (<1)	4 (1)	15 (2)	37 (2)	2 (1)	54 (2)	40 (2)
ALT or AST increased ^a	2	4	10	21	1	32	22
Neutrophils decreased ^b	-	-	3	6	1	10	8
Bilirubin increased ^c	-	-	2	7	-	9	4
Platelet count decreased ^d	-	-	-	1	-	1	2
Triglycerides increased	-	-	-	-	-	-	2
Platelet count increased	-	-	-	-	-	-	1
Weight increased	-	-	-	-	-	-	1
Eosinophilia	-	-	-	1	-	1	-
PPD positive	-	-	-	1	-	1	-
Hemoglobin decreased	1	-	-	-	-	-	-
Infections and Infestations							
Total patients with at least one AE	7 (1)	1 (<1)	5 (1)	8 (<1)	1 (<1)	14 (<1)	24 (1)
Pneumonia	2	-	2	1	1	4	7
Empyema	-	-	-	1	-	1	1
Cellulitis	-	-	-	2	-	2	3
Diverticulitis	-	-	-	-	-	-	2
Respiratory tract infection	-	1	1	-	-	1	2
Appendicitis	-	-	-	-	-	-	1
Intra-abdominal abscess	-	-	-	1	-	1	1
Sepsis, pulmonary	1	-	-	1	-	1	1
Osteomyelitis	1	-	1	-	-	1	1
Dermatitis infection	-	-	-	1	-	1	-
Septic arthritis	-	-	-	1	-	1	-
Pyelonephritis, acute	-	-	-	1	-	1	-
Pneumocystis jiroveci	-	-	1	-	-	1	-
Mycobacterium Avium Intracellulare	-	-	-	-	-	-	1
Tuberculosis	-	-	-	-	-	-	1
Nasopharyngitis	-	-	-	-	-	-	1
Varicella	-	-	-	-	-	-	1
Urinary tract infection	1	-	-	-	-	-	1
Wound infection	-	-	-	-	-	-	1
Post-procedural infection	1	-	-	-	-	-	-
Purulent discharge	1	-	-	-	-	-	-
Neoplasms, benign/malign/NOS							
Total patients with at least one AE	1 (<1)	3 (1)	1 (<1)	0	1 (<1)	2 (<1)	27 (1)
Lung cancer ^e	-	1	-	-	-	-	7
Breast cancer	-	-	-	-	-	-	3
Gastric cancer	-	-	-	-	1	1	2
Colon cancer	-	1	-	-	-	-	2
Prostate cancer	1	-	-	-	-	-	2
Cervical cancer	-	-	1	-	-	1	1
Colon neoplasm	-	-	-	-	-	-	1
Diffuse large B-cell lymphoma	-	-	-	-	-	-	1
Glioblastoma	-	-	-	-	-	-	1
Lymphoproliferative disorder	-	-	-	-	-	-	1
Meningioma	-	-	-	-	-	-	1
Metastatic neoplasm	-	-	-	-	-	-	1
Metastatic squamous cell carcinoma	-	-	-	-	-	-	1
Ovarian cancer	-	-	-	-	-	-	1
Squamous cell carcinoma	-	-	-	-	-	-	1
Uterine cancer	-	-	-	-	-	-	1
T cell lymphoma	-	1	-	-	-	-	-

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

Multiple occurrences of the same AE in one individual are counted only once

Events on escape therapy are excluded

a) includes preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal

b) includes Blood and Lymphatic System Disorders preferred terms of neutropenia and leukopenia

c) includes Hepatobiliary Disorders preferred term of hyperbilirubinemia

d) includes Blood and Lymphatic System Disorders preferred term of thrombocytopenia

e) includes preferred terms: lung adenocarcinoma, lung adenocarcinoma metastatic, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified, non-small cell lung cancer, small cell lung cancer stage unspecified

Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, Part 2 of 3							
	6-months pooled safety population						Long term safety population
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients discontinuing due to AE	29 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discontin.	29	15	38	75	11	124	159
Gastrointestinal Disorders							
Total patients with at least one AE	1 (<1)	5 (2)	1 (<1)	11 (1)	1 (<1)	13 (<1)	15 (1)
GI perforation ^f	-	-	-	2	1	3	3
Abdominal pain	-	-	-	1	-	1	2
Dyspepsia/gastritis/GERD	-	-	-	2	-	2	2
GI ulcer ^g	1	-	-	2	-	2	1
Stomatitis/Mouth ulcer	-	1	-	2	-	2	1
GI bleeding ^h	-	1	1	-	-	1	2
Diarrhea	-	-	-	-	-	-	2
Irritable bowel syndrome	-	-	-	-	-	-	1
Colitis ischemic	-	-	-	-	-	-	1
Pancreatitis	-	-	-	1	-	1	-
Sigmoiditis	-	-	-	1	-	1	-
Crohn's disease	-	2	-	-	-	-	-
Nausea	-	1	-	-	-	-	-
Skin and Subcutaneous Tissue							
Total patients with at least one AE	1 (<1)	0	3 (<1)	6 (<1)	0	9 (<1)	9 (<1)
Rash	-	-	-	-	-	-	2
Dermatitis	-	-	1	-	-	1	1
Urticaria	-	-	-	1	-	1	1
Alopecia	-	-	1	-	-	1	1
Cutaneous vasculitis	1	-	-	1	-	1	1
Blister/skin ulcer	-	-	-	1	-	1	1
Skin fragility	-	-	-	-	-	-	1
Skin lesion	-	-	-	-	-	-	1
Erythema multiforme	-	-	-	1	-	1	-
Pyoderma gangrenosum	-	-	-	1	-	1	-
Pruritis	-	-	-	1	-	1	-
Drug eruption	-	-	1	-	-	1	-
Respiratory/Thoracic/Mediastinal							
Total patients with at least one AE	1 (<1)	0	1 (<1)	1 (<1)	0	2 (<1)	11 (<1)
Interstitial lung disease	-	-	-	-	-	-	2
Pulmonary fibrosis, idiopathic or NOS	-	-	-	1	-	1	2
Asthma	-	-	-	-	-	-	1
COPD	-	-	-	-	-	-	1
Dyspnea	-	-	-	-	-	-	1
Pleural effusion	-	-	-	-	-	-	1
Pneumonitis	-	-	-	-	-	-	1
Pulmonary embolism	-	-	-	-	-	-	1
Acute respiratory distress syndrome	-	-	-	-	-	-	1
Rheumatoid lung	-	-	1	-	-	1	-
Wegener's granulomatosis	1	-	-	-	-	-	-
Immune System Disorders							
Total patients with at least one AE	0	1 (<1)	3 (<1)	3 (<1)	0	6 (<1)	3 (<1)
Anaphylactic reaction	-	-	2	1	-	3	2
Hypersensitivity	-	-	1	2	-	3	1
Sarcoidosis	-	1	-	-	-	-	-
Nervous System Disorders							
Total patients with at least one AE	2 (<1)	0	1 (<1)	3 (<1)	1 (<1)	5 (<1)	4 (<1)
Axonal neuropathy	-	-	-	-	-	-	2
Demyelination	-	-	-	-	-	-	1
Migraine	-	-	-	1	-	1	1
CVA	-	-	-	1	-	1	-
Hemorrhagic stroke	-	-	-	1	-	1	-
Headache	-	-	-	-	1	1	-
Syncope	-	-	1	-	-	1	-
Facial palsy	1	-	-	-	-	-	-
Paresthesia	1	-	-	-	-	-	-

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

Multiple occurrences of the same AE in one individual are counted only once

Events on escape therapy are excluded

f) includes preferred terms: diverticular perforation, gastrointestinal perforation, large intestine perforation

g) includes preferred terms: duodenal ulcer, gastric ulcer, large intestinal ulcer

h) includes preferred terms: rectal hemorrhage, melena, GI hemorrhage

i) includes preferred terms: rheumatoid vasculitis, vasculitis, vasculitis necrotising

Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

Adverse Events Causing Discontinuation in the Tocilizumab RA Pivotal Studies and Long-Term Extensions by Body System and Trial Treatment, Part 3 of 3							
	6-months pooled safety population						Long term
	Placebo + DMARD*	MTX	TCZ 4mg/kg + MTX	TCZ 8mg/kg + DMARD*	TCZ 8mg/kg	All TCZ	<u>safety population</u> Pooled TCZ
Enrolled	1170	284	774	1582	288	2644	2562
Total patients discontinuing due to AE	29 (2)	15 (5)	38 (5)	74 (5)	11 (4)	123 (5)	158 (6)
Total number of AEs causing discont.	29	15	38	75	11	124	159
Cardiac Disorders							
Total patients with at least one AE	1 (<1)	0	0	1 (<1)	1 (<1)	2 (<1)	6 (<1)
Myocardial infarction/AMI	-	-	-	-	-	-	3
Cardiac failure	-	-	-	-	-	-	1
Aortic valve stenosis	-	-	-	-	-	-	1
Palpitations	-	-	-	-	-	-	1
Acute coronary syndrome	-	-	-	1	-	1	-
Myocardial ischemia	-	-	-	-	1	1	-
Coronary artery thrombosis	1	-	-	-	-	-	-
Hepatobiliary Disorders							
Total patients with at least one AE	0	0	0	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Cholecystitis, acute	-	-	-	-	1	1	1
Hepatic steatosis	-	-	-	-	-	-	2
Hepatotoxicity	-	-	-	1	-	1	-
Liver disorder	-	-	-	-	1	1	-
Vascular Disorders							
Total patients with at least one AE	2 (<1)	0	1 (<1)	0	0	1 (<1)	4 (<1)
Vasculitis ⁱ	-	-	-	-	-	-	3
Deep vein thrombosis	2	-	1	-	-	1	1
Musculoskeletal and Connective Tissue							
Total patients with at least one AE	6 (<1)	0	2 (<1)	0	1 (<1)	3 (<1)	2 (<1)
Rheumatoid arthritis flare	4	-	2	-	-	2	2
Systemic Lupus Erythematosus	-	-	-	-	1	1	-
Pseudoarthrosis	1	-	-	-	-	-	-
Rheumatoid nodule	1	-	-	-	-	-	-
General Disorders/Admin. Site							
Total patients with at least one AE	3 (<1)	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Infusion related reaction	1	-	-	1	1	2	-
Chest discomfort/pain (non-cardiac)	-	-	1	-	-	1	1
Pyrexia	2	-	-	-	-	-	-
Pregnancy/Puerperium/Perinatal							
Total patients with at least one AE	1 (<1)	0	1 (<1)	0	0	1 (<1)	3 (<1)
Pregnancy	1	-	-	-	-	-	3
Induced abortion	-	-	1	-	-	1	-
Injury/Poison./Procedural Complic.							
Total patients with at least one AE	0	0	1 (<1)	2 (<1)	0	3 (<1)	1 (<1)
Fall	-	-	1	1	-	2	-
Femur fracture	-	-	-	1	-	1	-
Joint dislocation	-	-	-	-	-	-	1
Psychiatric Disorders							
Total patients with at least one AE	0	1 (<1)	0	0	0	0	2 (<1)
Completed suicide	-	-	-	-	-	-	1
Depression	-	-	-	-	-	-	1
Schizophrenia	-	1	-	-	-	-	-
Renal and Urinary Disorders							
Total patients with at least one AE	0	0	0	0	0	0	2 (<1)
Renal failure acute	-	-	-	-	-	-	1
IgA nephropathy, proliferative	-	-	-	-	-	-	1
Blood and Lymphatic System Disorders							
Total patients with at least one AE	0	0	1 (<1)	0	0	1 (<1)	0
Lymphadenopathy	-	-	1	-	-	1	-
Metabolism and Nutrition Disorders							
Total patients with at least one AE	0	0	1 (<1)	0	0	1 (<1)	0
Gout	-	-	1	-	-	1	-

* Includes MTX

Data cut-off April 20, 2007 for 6 month safety population; October 1, 2007 for long-term safety population

Multiple occurrences of the same AE in one individual are counted only once

Events on escape therapy are excluded

i) includes preferred terms: rheumatoid vasculitis, vasculitis, vasculitis necrotising

Adapted from stae11_wd of Module 2.7.4 Summary of Clinical Safety and Table stae11_wd from 120 d safety update

Table 34 GI Perforations Line Listing

GI Perforations in the Tocilizumab Global Program								
Study	Event	Age/ Gender	TCZ dose	Doses prior to event	Latency (months)	Concomitant medications	Outcome	Comments
Roche Tocilizumab RA Pivotal Studies								
UGI Perforations								
WA17824	Duodenal perforation	76/F	8 mg/kg	2	1	ranitidine	death	
LGI Perforations								
WA18062	Diverticular perforation	82/F	8 mg/kg	2	1	pred/mtx	resolved	withdrawn
WA18063	Diverticular perforation	65/M	8 mg/kg	5	4	pred/mtx/asa salicylamide	resolved	withdrawn
WA18063/18696	Diverticular perforation	50/M	8 mg/kg	23	21	mtx/ssa/naproxen	resolved	withdrawn
WA18062/18696	Diverticular perforation abdominal wall abscess small bowel ischemia	60/F	8 mg/kg	8	8	mtx/pred	death	
WA18063/18696	Sealed divertic. perf.	65/F	8 mg/kg	18	21	mtx/pred/ssa ketoprofen/oxaprozin	resolved	
WA18063/18695	Diverticular perforation	67/F	8 mg/kg	33	31	mtx/pred	resolved	withdrawn
WA17822/18695	Diverticular perforation	67/M	8 mg/kg	28	27	mtx/pred	resolved	withdrawn
WA17823	Diverticular perforation abdominal abscess	66/F	blinded	11	9.5	indomethacin	resolved	withdrawn
WA18062/18696	Colon necrosis/perf.	48/F	4-8 mg/kg	19	24	mtx/pred diclofenac/tramadol	unknown	withdrawn
WA17823	Acute abdomen/free air	50/F	4-8 mg/kg	10	15	mtx/pred	resolved	unk source
Chugai Tocilizumab Studies								
UGI Perforations								
MRA012JP (RA)	Esophageal perforation (iatrogenic)	65/F	8 mg/kg	13	11	pred/lornoxicam	resolved	continued
MRA010JP (RA)	Duodenal perforation Sigmoid perforation	49/F	8 mg/kg	37	36	pred/etodolac teprenone	resolved/ improved	withdrawn
MRA011JP (SJIA)	Duodenal perforation	10/M	2-4-8 mg/kg q2wk	23	10.5	corticosteroids NSAIDs, PPIs	resolved	withdrawn
MRA006JP (Castleman's)	Gastric perforation	56/M	2-4-8 mg/kg q2wk	169	49	corticosteroids loxiprofen/famotidine	improved	continued
LGI Perforations								
MRA010JP (RA)	Sigmoid perforation		see above					
MRA214JP (RA)	Sigmoid perforation abdominal abscess	45/F	8 mg/kg	28	26	pred/diclofenac	resolved	withdrawn
Compassionate- use (RA)	Sigmoid perforation from diverticulitis	59/F	range	52	48	corticosteroids diclofenac/DMARDs	resolved	continued
MRA008JP (Crohn's)	Intestinal perforation	24/M	8 mg/kg q2wk	2	1	corticosteroids	resolved	pre-event colo;withdrawn

Source: Section 3.9.3.3 and Table 13 of 120 day safety update