CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125472Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 30, 2013
From	Banu A. Karimi-Shah, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 125472
Applicant	Genentech
Date of Submission	December 21, 2012
PDUFA Goal Date	October 21, 2013
Proprietary Name / Established (USAN) names	Actemra®/tocilizumab
Dosage forms / Strength	Pre-filled syringe/162 mg
Proposed Indication(s)	Moderately to Severely Active Rheumatoid Arthritis in Adults with an Inadequate Response to one or more DMARD therapies (b) (4)
Recommended:	*Approval, with revisions to proposed labeling*

1. Introduction

Genentech submitted Biologic Licensing Application (BLA) 125472 on December 21, 2012, in support of subcutaneous (SC) administration of tocilizumab (TCZ) in adult rheumatoid (RA) patients. Tocilizumab for intravenous (IV) infusion was first approved in the United States in January 2010 (BLA 125276) for the treatment of moderately to severely active RA patients who have had an inadequate response to one or more TNF antagonists, and received subsequent approval for the broader group of RA patients who have had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Subsequently, tocilizumab IV was also approved for systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic arthritis (pJIA) in April 2011 and April 2013, respectively. It is the first in class (IL-6 receptor antagonist) biologic agent for treatment of adult patients with RA, and pediatric patients with sJIA and pJIA, approved in the United States.

Tocilizumab is a recombinant human monoclonal antibody targeting the interleukin-6 receptor (IL-6R). Tocilizumab selectively binds to soluble and membrane-bound human IL-6R, thereby inhibiting the binding of IL-6 to its receptors and blocking the subsequent downstream signaling cascade associated with IL-6. It is currently marketed as a solution for intravenous infusion, to be administered over 60 minutes. For RA, the current IV dosing is 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. For pJIA, the currently approved IV dosing is 10 mg/kg given once every 4 weeks for patients weighing < 30 kg, and 8 mg/kg for patients weighing ≥30 kg. For sJIA, the currently approved IV doing is 12 mg/kg given once every 2 weeks for patients < 30 kg, and 8 mg/kg for patients ≥ 30 kg.

This BLA consists of data to support the applicant's proposed marketing of tocilizumab as a fixed dose (162 mg) subcutaneous injection in pre-filled syringes to be given once weekly in adult RA patients weighing ≥100 kg, and once every other week in patients weighing <100 kg, increasing to once per week based on clinical response. The proposed indication for the fixed dose subcutaneous formulation is the same as the currently approved RA indication for intravenous tocilizumab.

The clinical efficacy and safety data that supported the original approval of tocilizumab for the claim of reducing signs and symptoms (clinical response), inhibiting progression of structural damage (radiographic response), and improving physical function and health-related outcomes in RA were from five controlled clinical studies in patients 18 years of age and older with active RA. These studies are described in the currently approved tocilizumab product label. The current submission to support approval of subcutaneous administration of tocilizumab is based on one non-inferiority study comparing the efficacy and safety of tocilizumab subcutaneous and intravenous dosing (WA22762 or SC-I), one placebo-controlled superiority study (NA25220 or SC-II), as well as long-term open label extensions of these studies. Six new PK studies were also conducted.

An efficacy supplement was initially submitted on December 21, 2012, for TCZ SC and was filed as a standard review. It was verified with Mike Jones in the Office of Regulatory Policy, that based upon the bundling policy (Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (found here: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf), products that are not qualitatively and quantitatively alike should be submitted in separate original applications. As such, tocilizumab SC was submitted under a new BLA number (125472) [Tocilizumab IV BLA Number: 125276].

2. Background

Expectations for the subcutaneous tocilizumab clinical development program were discussed during several key interactions with the Agency. The discussion and/or advice/ recommendations of the Agency are outlined below.

- March 2010, Denial of Special Protocol Assessment for WA22762:
  - The sponsor should meet the 10% non-inferiority margin with similar or better safety in order for the SC route of administration to be incorporated into the label (b) (4)
  - The sponsor should assess efficacy in per-protocol and intent-to-treat populations. We expressed concern regarding the limited information in the protocol regarding how protocol violations or patient discontinuations may affect the efficacy evaluation in either the PP or ITT populations.
  - The sponsor should add a continuous efficacy outcome measure (ACR-Hybrid) as an exploratory endpoint.
  - The sponsor should monitor PK over a wide range of body weights, as there was a high variability in systemic tocilizumab levels.

  - The sponsor should evaluate all cases of anaphylaxis in the SC development program using NIAID/FAAN 2006 criteria.

- March 2010, Denial of Special Protocol Assessment for NA25220:
  - The Agency expressed concerns regarding using historical IV data to support bridging.
  - The sponsor should include a radiographic assessment at week 24.

- February 2012, Written Response:
  - Given fixed dosing in SC, the sponsor should include patients at the extremes of body weight.
  - The Agency could not agree (b) (4)

- October 2012, pre-BLA meeting:
  - The sponsor reported that no data sets would be submitted for the Japanese studies, but that analysis plans and actual analyses would be provided.
  - General agreement was reached regarding the sponsor's proposal to request a waiver in children with pJIA < 2 years old, and a deferral for pJIA in children ≥ 2 years for the SC formulation.

3. CMC/Device

Primary product quality reviewer: Gerald Feldman, Ph.D.
Product quality team leader: Marjorie Shapiro, Ph.D.

The recommended action from a CMC/Quality perspective is Approval.

- **General product quality considerations**

This BLA is submitted to support the approval of a 162 mg pre-filled syringe (PFS) dosage form for subcutaneous administration of tocilizumab. The currently approved dosage from is a solution in single-use vials for intravenous infusion. Tocilizumab for subcutaneous administration is supplied as a sterile, colorless to slightly yellowish, preservative-free liquid solution in a single-use, 1 mL prefilled syringe, delivering 162 mg tocilizumab/0.9 mL. The composition of the drug product is 180 mg/mL tocilizumab in (b) (4) arginine, (b) (4) methionine, (b) (4) histidine and (b) (4) (w/v) polysorbate 80, and has a pH 6.0. The tocilizumab drug substance manufacturing process (b) (4) Adequate data were provided to support the requested shelf life of 30 months for (D) (4) storage of the tocilizumab PFS when stored at 2-8° C.

The Sponsor requested a categorical exclusion form the preparation of an environmental assessment based on 21 CFR 25.21(a) and (b), which was deemed acceptable.

- **Facilities review/inspection**

The drug product will be supplied in a pre-filled syringe sealed with a rigid needle shield (RNS) and a needle safety device (NSD). It is manufactured by (b) (4) . Labeling, assembly with the NSD, and secondary packaging are performed by F. Hoffman-La Roche Ltd in Kaiseraugst, Switzerland. An inspection waiver was issued for (b) (4) An inspection was conducted for F. Hoffmann-La Roche Ltd. by CIN-DO on July 22-25, 2013. A 4-observation 483 was issued. The initial recommendation was Voluntary Action Indicated (VAI). However, CDRH has deferred to CDER, the lead center for this inspection, to initiate any follow-up actions to the violations found during the inspection and to make the final decision on the overall classification of the inspection. The decision from CDER OC is pending at the time of this memorandum and will be discussed in the Division Director's review.

- **Other notable issues (resolved or outstanding)**

The CMC review team has determined that the submitted information is adequate to support approval of this BLA. No post-marketing requirements or commitments are recommended from a quality standpoint. Labeling of the package insert, carton, and container were found to be acceptable.

The Division consulted the Center for Devices and Radiological Health (CDRH) to assist in the review of the PFS configuration and components. Completion of the CDRH review of the PFS is pending at the time of this memorandum and will subsequently be discussed in the Division Director's review. CDRH was also consulted to review human factor evaluations. The evaluation of the human factors studies showed that IFU changes were effective in reducing the task failures and use errors seen in the previous study. Therefore, CDRH determined the human factors data acceptable and has no outstanding concerns.

4. Nonclinical Pharmacology/Toxicology

Primary pharmacology/toxicology reviewer: Asoke Mukherjee, Ph.D.
Pharmacology/toxicology supervisor: Timothy Robison, Ph.D.

The bulk of the information regarding the toxicologic profile of subcutaneous (SC) tocilizumab is derived from the nonclinical program conducted to support chronic intravenous (IV) administration for the approved adult RA indication. The Applicant submitted two nonclinical studies to bridge over to the subcutaneous route of administration. To bridge toxicity characterized by the intravenous route, the sponsor conducted a 9-week subcutaneous bridging toxicity study in cynomolgus monkey that received a SC dose of 100 mg/kg/week. No treatment-related local effects were observed in the cynomolgus monkeys and the NOAEL was 100

mg/kg/SC. The margin of safety for the proposed clinical dose at 162 mg/SC q 2week (2.7 mg/kg) was 37 on the basis of mg/kg doses. I n a mini-pig model, the SC dose of 180 mg was found to be bioequivalent to the identical IV dose.

- **General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise)**

The non-clinical data for the application were supported by the previous BLA 125276 for IV tocilizumab. In the pivotal 6-month repeat dose toxicity study of tocilizumab with cynomolgus monkeys that received doses of 1, 10, and 100 mg/kg/ week by IV infusion, granuloma of liver and skeletal muscle degeneration were observed at 10 and 100 mg/kg IV. The NOAEL was identified as the low dose of 1 mg/kg based upon findings at higher doses.

- **Carcinogenicity**

A carcinogenicity waiver request was reviewed under BLA 125276. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

- **Reproductive and developmental toxicology**

In an embryo-fetal developmental toxicity study with pregnant cynomolgus monkeys that were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg per kg from gestation days 20-50, increased incidences of abortion/embryo-fetal death were observed at 10 and 50 mg/kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg IV with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab at 50 mg/kg IV once every 3 days showed no impairment of fertility. Tocilizumab is pregnancy category C.

- **Other notable issues (resolved or outstanding)**

The pharmacology/toxicology review team has determined that the submitted information is adequate to support approval of this BLA. No post-marketing requirements or commitments are recommended from a non-clinical standpoint.

Non-clinical labeling revisions are proposed to conform to the most current CFR format (Indications and Usage changed on April 29, 2013 and Sections 8.1, 8.3, 12.1, and 13.1). Proposed labeling revisions in the nonclinical sections also take recommendations from the Maternal Health Team into consideration, in order to comply with the pending Pregnancy and Lactation Labeling Rule. These sections of the label were updated per the pharm/tox team's recommendations and were accepted by the Applicant.

5. Clinical Pharmacology/Biopharmaceutics

Primary Clinical Pharmacology/Pharmacometrics Reviewer: Liang Zhao, Ph.D.
Clinical Pharmacology Supervisor: Satjit Brar, Ph.D.

- **General clinical pharmacology/biopharmaceutics consideration, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The PK data in this submission are derived primarily from the two pivotal phase 3 clinical trials in patients with RA (WA22762 and NA25220) as well as six clinical pharmacology studies that were designed to characterize the PK and PD profiles of tocilizumab following IV and SC administration, and to evaluate the immunogenicity of tocilizumab when administered SC.

Population PK and exposure-response analysis
Based on the population PK analysis, the bioavailability of tocilizumab following SC administration for a typical patient was estimated to be 79.5% (95%CI: 77.9 – 81.1%). Following SC dosing in rheumatoid arthritis patients, the absorption half-life was around 3-5 days. The $t_{1/2}$ of tocilizumab is concentration dependent. For IV administration, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For SC administration, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

Among all covariate relationships for PK exposure, body weight was identified as the single covariate that significantly influenced TCZ clearance (CL) and volume parameters. Corresponding to a body weight range of 40 and 140 kg, CL decreased and increased respectively by 25% and 47%, and volumes decreased and increased respectively by 32% and 61% relative to the value corresponding to a patient weighting 70 kg.

Dose Selection Rationale
The SC dose regimens for the two phase 3 studies (WA22762 and NA25220) were determined based on PK, PD, and safety data from two phase 1/2 studies (MRA227JP and NP22623) in patients with RA. Based on these two study results, it was found that the PD profiles (CRP, ESR, and sIL-6R) corresponding to the tocilizumab 162 mg SC QW regimen were most comparable to those following the tocilizumab 8 mg/kg IV Q4W regimen. In comparison, the162 mg SC Q2W regimen led to slower and less pronounced PD responses than 8 mg/kg IV Q4W and 162 mg SC QW regimens. However, the PD responses following the 162 mg SC Q2W regimen were superior to the 81 mg SC Q2W and QW regimens.

Based on phase 3 study results, tocilizumab 162 mg SC QW and 8 mg/kg IV Q4W treatment regimens demonstrated comparable efficacy. The tocilizumab 162 SC Q2W dosing regimen also showed clinically superior efficacy improvements to placebo. However, the treatment effect was less pronounced in patients weighing > 100 kg weight group treated with tocilizumab 162 kg SC Q2W treatment compared to the same body weight groups for tocilizumab 162 kg SC QW and 8

mg/kg IV Q4W treatments (50.0%, 50.8%, 38.5%, and 27.3% for 162 mg SC QW, 162 mg SC Q2W, 8 mg/kg IV Q4W, and placebo in terms of ACR20 responses, respectively, at Week 24 in ITT population). By directly comparing the ACR20 responses of patients weighting > 100 kg between SC QW and SC Q2W treatments (i.e., 50.0 % vs. 38.5%), the decreased ACR responses for 162 mg SC Q2W treatment is likely to be associated with less drug exposure. In addition, it was reported that a substantial % of escape patients who escalated from the Q2W SC regimen to the QW SC regimen showed an improvement in efficacy. Therefore, dose escalation from SCQ2W to SC QW for patients weighing > 100 kg to gain therapeutic advantage is reasonable. Similarly, there is adequate clinical data to support the starting dosing regimen of 162 mg SC Q2W for patients weighing <100 kg. The ACR20 response was similar for both dosing regimens in patients weighing < 100 kg (>60%).

In terms of safety, both the exposure safety model and the clinical studies demonstrated a higher safety risk for the SC QW versus the SC Q2W dosing regimen. In general, adverse events occurred in a higher percentage of patients treated with the SC QW dosing regimen. Specifically, grades 1 and 2 neutropenia were more common in the SC QW group as compared with SC Q2W group. Review of AES leading to dose modifications/interruption in studies WA22762 and NA25220 until Week 24 and clinical cutoff in the safety population showed that the incidence of such events was higher in the SC QW treatment than in the SC Q2W treatment (27.3% vs. 13.5% at Week 24 and 36.1% vs. 16.7% at clinical cutoff) [See Section 8 for more details regarding the safety of the two SC dosing regimens].

Taking into account that both the exposure safety model and the clinical studies demonstrated a higher safety risk for the SC QW versus the SC Q2W dosing regimen, starting with the more lower (more infrequent) dosing regimen, as is done with the IV dosing, is reasonable.

- **Pathway of elimination**

As a large protein molecule, tocilizumab is most likely cleared by reticuloendothelial system.

- **Critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment**

Body weight was identified as the single covariate that significantly influenced tocilizumab clearance and volume parameters. Corresponding to a body weight range of 40 and 140 kg, clearance decreased and increased respectively by 25% and 47%, and volumes decreased and increased respectively by 32% and 61% relative to the value corresponding to a patient weighting 70 kg.

- **Thorough QT study or other QT assessment**

As a macromolecule, unlikely to affect the cardiac conduction system, a thorough QT study was not required for the IV or SC tocilizumab programs.

- **Immunogenicity**

Consistent with the immunogenicity rate reported for tocilizumab IV, the overall immunogenicity rate for tocilizumab SC was low (~1%). As inferred from population PK analysis based on data from the two phase 3 studies (WA22762 and NA25220), the linear portion of clearance showed no appreciable difference between anti-tocilizumab antibody positive and negative patients. In the population exposure–response analyses of the relationships between exposure and DAS28 and between exposure and neutrophil count, neutralizing anti-tocilizumab antibodies were not identified as a covariate influencing either tocilizumab efficacy or safety.

- **Other notable issues (resolved or outstanding)**

The clinical pharmacology review team has determined that the submitted information is adequate to support approval of this BLA. No post-marketing requirements or commitments are recommended from the clinical pharmacology standpoint. Minor labeling revisions were proposed to the clinical pharmacology sections of the label. These recommendations were accepted by the Applicant.

6. Clinical Microbiology

Primary Microbiology Reviewer: Maria Candauchacon, Ph.D.
Microbiology Team Leader: Patricia Hughes, Ph.D.

Both the drug substance and drug product sections of this BLA submission were reviewed from a microbial control, CMC sterility assurance, and microbiology quality perspective, and were found to be acceptable. From a microbial control and microbiology product quality perspective, this supplement is recommended for approval.

Microbiology PMCs:
1. The sponsor has agreed that they will determine the (b) (4) volume necessary for (b) (4) and will provide the report by October 30, 2013.

7. Clinical/Statistical- Efficacy

Primary Clinical Reviewer: Miya Paterniti, M.D.
Primary Statistical Reviewer: David Hoberman, Ph.D.
Statistical Team Leader: Joan Buenconsejo, Ph.D.

Overview of the clinical program

The clinical program to support the fixed dose subcutaneous administration of tocilizumab (TCZ) consisted primarily of two phase 3, randomized, double-blind, controlled trials of tocilizumab in 1,918 (SC = 1068; IV = 850) adult RA patients with moderately to severely active disease who have had an inadequate response to one or more DMARDs. Study WA22762 (or SC-I) was a non-inferiority study comparing TCZ SC 162mg qw to TCZ IV 8mg/kg q4w. Study NA25220 (or SC-II) was a superiority study comparing TCZ SC 162mg q2w to placebo. All treatment arms included a background of DMARD therapy. The efficacy data was provided from the 24-week controlled period of each study. Both studies also included 72-week long-term extension periods, which are listed separately in the table below (see Table 1).

Table 1: Summary of Clinical Program for Tocilizumab SC

Study [Sites]	Design	Study duration	Treatment[†]	N	Study Population	Endpoints
Pivotal efficacy and safety studies						
WA22762 [25 countries] **(SC-I)**	R, DB, AC	24 weeks	TCZ 162 mg SC qw TCZ 8 mg/kg IV q4w	631 631	Moderate to Severely Active RA Age: 18-86 (53)	ACR20 response (non-inferiority)
NA25220 [21 countries] **(SC-II)**	R, DB, PC	24 weeks	TCZ 162 mg SC q2w Placebo SC q2w Escape at ≥ 12 weeks TCZ 162 mg SC q2w	437 219 162	Moderate to Severely Active RA Age: 18-82 (52)	ACR20 response
Long-Term Extensions[1]						
WA22762-LTE	OL, R	72 weeks	TCZ 162 mg SC qw TCZ 8 mg/kg IV q4w IV-SC switch SC-IV switch	524 377 186 48	Moderate to Severely Active RA Age: 18-86 (53)	Safety
NA25220-LTE	OL, R	72 weeks	TCZ 162 mg SC q2w TCZ 162 mg SC q2w to AI PBO to TCZ 162 mg SC q2w PBO to TCZ 162 mg SC q2w AI Escape Therapy: TCZ 162 mg SC qw PFS/AI	167 168 61 59 7	Moderate to Severely Active RA Age: 18-82 (52)	Safety

TCZ: tocilizumab; R: randomized; DB: double-blind; AC: active control; PC: placebo control; OL: open label; PFS: pre-filled syringe; AI: autoinjector (not being proposed in this application).
1: All long-term extensions were ongoing at the time of submission. Clinical data cut-off was January 2012.
All SC treatments were via PFS unless otherwise specified.
All patients had inadequate response to DMARDs and were being treated with concomitant non-biological DMARD background therapy.

The efficacy evaluation focuses on the controlled 24-week treatment periods of studies WA22762 and NA25220. The long-term extension portion of these studies will be addressed in the safety discussion.

Study design and conduct

- *Non-inferiority study (WA22762 or SC-I)*

Study WA22762 was a randomized, double-blind, double-dummy, active-controlled, parallel group, global study (209 sites in 25 countries) conducted in patients with active RA having an inadequate response to DMARDs. After meeting eligibility criteria, 1262 patients were randomized in 1:1 ratio to receive either tocilizumab 162 mg SC weekly or tocilizumab IV 8 mg/kg every 4 weeks. Patients were stratified by weight (<60 kg, 60-100kg, >60 kg) region, and remained on background DMARD therapy. The primary efficacy endpoint was the proportion of patients achieving ACR20 response at Week 24, with the primary analysis being a comparison between subcutaneous and intravenous tocilizumab in the per protocol population. Study WA22762 was designed to determine the non-inferiority of the SC regimen with a non-inferiority margin of 12% using the ACR20 at 24 weeks as the primary endpoint. Non-inferiority of tocilizumab SC was claimed if the lower bound of the adjusted 95% CI for the difference between the response rates, tocilizumab SC minus tocilizumab IV, was not less than 12 percentage points. If this was met the 95% CI would then be tested against a 10% non-inferiority margin (NIM). The non-inferiority limits were defined to ensure maintenance of at least 65% (12% NIM) and 70% (10% NIM) of the ACR20 response seen with tocilizumab 8 mg/kg IV q4w versus placebo in the previous IV trials. The effect size of IV tocilizumab in previous placebo-controlled studies using the proportion of patients achieving ACR20 responses at 6 months was 48-60%. The non-inferiority margin was selected in agreement with previous Agency advice to the applicant. Other efficacy endpoints included ACR50 and ACR70 responses, physical function characterized by HAQ-DI, and changes in DAS28. Safety assessments included recording of adverse events, vital signs, clinical laboratory measures, physical examination, and immunogenicity. PK assessments were also conducted in a sub-study.

The mean age of the patient population was 53 years. A larger proportion of the randomized population was female (83%) and Caucasian (76%). The demographic parameters were fairly evenly split between the two treatment groups. Geographic region and body weight category were baseline stratification factors at randomization. The majority of the patients (67%) weighed between 60 and 100 kg, with 23% weighing < 60 kg and 10% weighing ≥100 kg. The treatment arms were balanced with respect to RA disease characteristics.

- *Placebo Controlled Study (NA25220 or SC-II)*

Study NA25220 was a randomized, double-blind, placebo-controlled, parallel group, global study (124 centers in 21 countries) conducted in patients with active RA having an inadequate response to DMARDs. After meeting eligibility criteria, 656 patients were randomized to receive either tocilizumab 162 mg SC or placebo every other week. From weeks 12 to 48, patients initially randomized to receive either tocilizumab or placebo could move to open label escape therapy with tocilizumab 162 mg SC once weekly if there was < 20% improvement in swollen joint count (SJC) and tender joint count (TJC) from baseline. The primary efficacy endpoint was the percentage of patients with ACR20 response at week 24. Other efficacy endpoints included ACR50 and ACR70 responses, physical function characterized by HAQ-DI, and change from baseline in the van de Heijde modified Sharp radiographic score at Week 24. Safety assessments were similar to Study WA22762.

The study population comprised predominantly Caucasian (72.1%) females (84.7%), with a mean age of approximately 52 years (range 18−82 years). The two treatment arms were balanced with respect to all baseline demographic characteristics recorded. The majority of the patients (67%) weighed between 60 and < 100 kg, with 27% weighing < 60 kg and 5.6% weighing ≥100 kg. Overall, the treatment arms were balanced with respect to RA disease characteristics.

Efficacy Results

The primary efficacy endpoint was ACR20 response at week 24, with the primary analysis being a comparison between the IV and SC tocilizumab per protocol populations in Study WA22762 (SC-I), with the NIM as described above; and IV tocilizumab versus placebo (ITT population) in Study NA25220. The primary efficacy results as well as some additional secondary endpoints are summarized in Table 2.

Table 2: Clinical Response in Studies SC-I and SC-II at Week 24

	SC-I[a]		SC-II[b]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8 mg/kg + DMARD N=537	TCZ SC 162 mg every other week + DMARD N=437	Placebo + DMARD N=219
ACR20				
No. Responders (%) [95% CI]	387 (69%) [66%, 73%]	394 (73%) [70%, 77%]	266 (61%) [56%, 65%]	69 (32%) [25%, 38%]
Weighted difference (95% CI)	-4% (-9.2, 1.2)		30% (22.0, 37.0)	
ACR50				
No. Responders (%) [95% CI]	262 (47%) [43%, 51%]	261 (49%) [44%, 53%]	174 (40%) [35%, 44%]	27 (12%) [8%,17%]
Weighted difference (95% CI)	-2% (-7.5, 4.0)		28% (21.5, 34.4)	
ACR70				
No. Responders (%) [95% CI]	134 (24%) [21%, 28%]	150 (28%) [24%, 32%]	86 (20%) [16%, 23%]	11(5%) [2%, 8%]
Weighted difference (95% CI)	-4% (-9.0, 1.3)		15% (9.8, 19.9)	
Change in DAS28 [Adjusted mean]				
	-3.5	-3.5	-3.1	-1.7
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7; -1.1)	
DAS28 < 2.6				
No. Responders (%) [95% CI]	198 (38%) [34%, 43%]	184 (37%) [33%, 41%]	111 (32%) [27%, 37%]	5 (4%) [1%, 7.5%]
Weighted difference (95% CI)	0.9 %(-5.0, 6.8)		28.6 (22.0, 35.2)	
HAQ-DI Response ≥ 0.3				
No. Responders (%) [95% CI]	336 (65%) [61%, 69%]	337 (67%) [63%, 71%]	202 (58%) [53%, 63%]	58 (47%) [38%, 56%]
Weighted difference (95% CI)	-2.3% (-8.1, 3.4)		12.1 (2.2, 22)	

a: Per Protocol Population; b: Intent to Treat Population

Results for SC and IV tocilizumab were essentially the same in study SC-I for ACR20/50/70 responders, and in the proportion of patients achieving an improvement of at least 0.3 units in the HAQ-DI. The pre-specified non-inferiority margin was met for ACR20 response, with the lower bound of the 95% confidence interval of the weighted difference in ACR20 responders being

-7.5. In Study SC-II, tocilizumab 162 mg every other week was superior to placebo. In general, the results were consistent with those seen for tocilizumab IV.

- ***Radiographic Response***

In study SC-II, the progression of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified total Sharp score (mTSS). At week 24, significantly less radiographic progression was observed in patients receiving tocilizumab SC every other week plus DMARD(s) compared to placebo; mean change from baseline in mTSS of 0.62 vs. 1.23, respectively, with an adjusted mean difference of -0.60 (-1.1, -0.1),. These results are consistent with those observed in patients treated with intravenous tocilizumab.

- ***Subgroup Analysis***

At week 24, the ACR20/50/70 responses in Study WA22762 were comparable for the SC qw and IV 8 mg/kg arms across the three body weight categories, with responses in both arms decreasing with increasing body weight. In Study NA25220, ACR responses with TCZ SC q2w also decreased with increasing body weight. Per Dr. Hoberman's analysis, logistic regression analysis showed that the overall response rate is slightly lower in those who weighed at least 100 kg compared to those who weighed between 60 and 100 kg. However, there was no evidence of any interaction between treatment and weight category.

The sponsor noted lower ACR responses in patients from North America compared with Europe, South America, and Rest of World. This was also noted by the Agency's statistical reviewer, Dr. Hoberman. Dr. Hoberman's logistic regression analysis showed that the overall response rate in North America was statistically significantly less than that in all other 3 regions. For Study NA25220, the overall response rate was also substantially lower in North America than the other regions (odds ratio=.26 compared to Europe). Per Dr. Hoberman, one possible explanation for this pattern in both trials emerges when the reasons for non-response are examined by region. There are three major reasons for nonresponse: 1) "withdrawals" due to lack of consent, adverse events, lost to follow up, etc., 2) finishing the trial but not fulfilling the ACR20 criteria for response, and 3) switching to "escape" therapy. Of the non-responders in the placebo group (Study NA25220), 6% were in category 1, 35% in category 2 and 59% in category 3. In the TCZ group, the respective percentages were 16%, 44%, and 40%. Examination of tables indicating percentages of each type of non-response by region in NA25220 indicates a tendency wherein North America has greater percentages of dropouts when summing the percentages of types 1 and 3. Thus, one reason for the lower response rates in North America may be different regional administrations of the trial regarding criteria for dropout.

- **Discussion of the statistical review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed**

The clinical and statistical review teams are in agreement that the data provided were adequate to provide substantial evidence that tocilizumab 162 mg SC weekly is non-inferior to the currently approved high dose IV tocilizumab dosing, and that tocilizumab 162 mg SC every other week was statistically better than placebo.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

There were no other notable efficacy issues.

8. Safety

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

The clinical review of safety is based primarily on data from the two pivotal studies: WA22762 (non-inferiority between TCZ SC QW and TCZ IV) and NA25220 (TCZ SC Q2w vs. placebo). The data reviewed comes from the 24-week controlled clinical trial periods as well as the open-label long-term extension periods for both studies (up to the cut-off of January 2012). SAEs that occurred after the clinical safety cut-off are also included. The safety profile of TCZ IV in adult RA is well-characterized. As such, data from the original clinical development program for the intravenous route of administration, including ongoing long-term extension studies, are incorporated into this review for comparison with the new SC data.

Safety data for this application includes pooled analyses from two pivotal phase 3 clinical trials with TCZ SC (WA22762 and NA25220) including their respective LTEs. The different treatment arms contributing to the pooled safety data base are described in below. Week 24 TCZ IV historical controls are added for comparison from the IV clinical development program, with updated pooled data from the LTEs of phase 3 clinical trials with TCZ IV in adult RA. The historical pooled TCZ IV all-exposure population is pooled from the studies shown in Table 3.

Table 3: Safety Database for SC and IV Tocilizumab

	Study WA22762			
	TCZ SC qw	TCZ 8mg/kg IV q4w	TCZ SC – IV Switch	TCZ IV-SC Switch
N (number of patients)	631	631	48	187

	Study NA25220					
	TCZ SC q2w	PBO	TCZ SC q2w to qw escape	PBO to TCZ SC qw escape	PBO to TCZ SC PFS q2w	PBO to TCZ SC AI q2w
N (number of patients)	437	219	72	90	61	59

	TCZ SC qw	TCZ SC q2w
Number of patients exposed to each group	908	557

→ All-exposure SC group (N=1465)

Core Study Protocol (Number of Patients)	Extension Protocol	Number of Patients Contributing IV TCZ Safety Data
WA18062 (N = 464) WA18063 (N = 1158) WA17824 (N = 618) WP18663 (N = 23)	WA18696 - ongoing (total treatment duration up to five years)	2263
WA17822 (N = 597)	WA18695 (total treatment duration up to five years)	597
WA17823 (N = 1149)	LTE phase included in main protocol (total treatment duration up to five years)	1149
WA19924 (N = 162)	N/A	162
Total number of patients in IV TCZ All-exposure Population		**4171**

IV = intravenous; LTE = long-term extension; TCZ = tocilizumab
All studies were Phase III, except for WP18663, which was a Phase I drug-drug interaction study.

The available total duration of exposure to IV TCZ treatment is much longer than the exposure to SC TCZ. Differences in exposure also exist between the different dose strengths and treatment groups within the same study. Therefore, for the purpose of comparing the risk of AEs across dose groups and routes of administration, the rate of events per patient years (PY) is used as a means of comparison. While the two dosing regimens (SC qw and SC q2w) are not included in the same study, this review evaluates the safety profiles of each regimen across studies.

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

Deaths
There were a total of 7 deaths reported during all periods of the submitted studies. During the controlled 24-week period, there was 1 death in the IV arm of WA22762 and there were three deaths in the SC treatment group of NA25220. In the LTEs, there was one additional death each in the SC and IV arms of WA22762, and one more death in NA25220 (in the TCZ PFS-to-TCZ AI switch arm. There were no deaths in the escape arms. The death rate per 100 PY of exposure in the all-exposure SC population (0.56 [95% CI: 0.18, 1.31]) was very similar to the death rate per 100 PY in the all-exposure IV population (0.58 [95% CI: 0.47, 0.71]).

Interestingly, the death rate per 100 PY at clinical cutoff was higher in the TCZ SC Q2W treatment arm (1.35, 95% CI [0.28, 3.95]), than in the TCZ SC QW treatment arm (0.22, 95% CI [0.01, 1.23]). Although the death rate in the TCZ SC q2W treatment arm was numerically higher, there were few deaths overall, making it difficult to draw definitive conclusions from this data. Deaths appeared to be related to known tocilizumab-associated toxicities, such as serious infection, or were consistent with comorbidities seen in the patient population such as underlying cardiovascular and pulmonary disease.

SAEs
During the 24 week treatment period, SAEs occurred with similar frequency when comparing SC and IV treatments arms and SC to historical IV controls. Of note, the rate of SAEs leading to withdrawal was higher in the TCZ SC qw arm in Study WA22762 (n=9, 1.4%), as compared with the TCZ q2w arm in Study NA25220 (n=4, 0.6%). The most common reasons for discontinuation were infections and laboratory abnormalities known to occur with tocilizumab. An overview of SAEs at clinical cutoff showed that the SAE event rate per 100 PY was slightly higher in the qw treatment arm vs. the q2w treatment arm (14.53 vs. 13.06, respectively). The SAE event-rate per 100 PY comparing SC all exposure and IV all exposure populations was similar at clinical cutoff.

Adverse Events of Special Interest
Adverse events of special interest identified in the adult RA population included infections (including serious and opportunistic infections, and tuberculosis), malignancies, anaphylaxis, hypersensitivity, injection site reactions, hepatic SAEs, stroke SAEs, myocardial infarction SAEs, bleeding SAEs, gastrointestinal perforations, and serious potential demyelinating disorders. For the majority of events, there were no notable differences between IV and SC tocilizumab. Notable exceptions include infections and hypersensitivity. The rate of infections per 100 PY was higher in the SC TCZ all-exposure population than in the IV TCZ all-exposure population (114.44, [95% CI: 107.53, 121.67] vs. 92.73 [95% CI: 91.25, 94.22], See Table 132 in Dr. Paterniti's review). However, the rates of serious infections, opportunistic infections, or fatal infections were similar for the SC and IV all-exposure populations. When comparing the rate of infections per 100 PY in the SC qw and SC q2w treatment arms, infections occurred more frequently in the SC qw group as compared with the SC q2w group (qw: 120.07, 95% CI[107.8, 133.3] vs. q2w: 96.34, 95% CI [82.6, 111.7]). Withdrawal due to infections was also slightly

more common in the SC qw group (1.1%) as compared with the SC q2w group (0.7%). Serious infections occurred with similar rates in both qw and q2w treatment arms.

With respect to hypersensitivity, the rates of all hypersensitivity reactions and clinically significant hypersensitivity reactions were numerically higher in the SC TCZ all-exposure population (15.77 (95% CI: 13.28, 18.60), 1.12 (95% CI: 0.54, 2.06), respectively) than in the IV TCZ all-exposure population (10.40 (95% CI: 9.91, 10.91), 0.38 (95% CI: 0.29, 0.48), respectively). However, only a small number of subjects in the TCZ SC population experienced serious hypersensitivity reactions (n =4) and serious clinically significant hypersensitivity reactions (n = 1). When comparing the two SC treatment arms, hypersensitivity reaction occurred more commonly in the SC qw group than in the SC q2w group, at both Week 24 and at clinical cutoff.

Adverse Events

Adverse events leading to discontinuation were more common in the SC qw treatment arm (event rate per 100 PY: 14.2, 95% CI [10.2, 19.2]), compared with the SC q2w treatment arm (event rate per 100 PY: 4.9, 95% CI [2.3, 9.4]), at week 24. A similar pattern of more frequent discontinuation in the SC qw group persisted when examined at clinical cutoff. In general, adverse events occurred more frequently in the SC qw group (76%) as compared with the SC q2w group (63%) at 24 weeks. The frequency of adverse events between SC qw and 8 mg/kg IV, and SC overall versus historical IV controls, was comparable. The most commonly reported AEs were infections and laboratory abnormalities known to occur with tocilizumab. The majority of AEs were Grade 1 or 2, and occurred more frequently in the SC qw group vs. the SC q2w group.

Adverse events (AEs) in the TCZ SC group were comparable to or lower than the TCZ IV group, including historical TCZ IV data, with the exception of injection site reactions (ISRs). ISRs occurred at a higher rate in the SC qw arm compared to IV and similarly in the SC q2w compared to placebo. Also, ISRs occurred more frequently in the SC qw group vs. the SC q2w group (number of events at 24 weeks: 168 vs. 57, respectively). The median duration of symptoms was short (3 days) and all ISRs were non-serious. None of the ISR AEs required treatment withdrawal, dose interruption or dose modification. There were no anaphylactic reactions and immunogenicity was low and similar to IV.

As mentioned in Section 5, Grade 1 and 2 neutropenia were seen more frequently in the SC qw group as compared with the SC q2w group. The SC development program, as submitted, showed that SC and IV TCZ laboratory profiles are similar.

In summary, the clinical development program does not raise any new safety concerns for subcutaneous tocilizumab. The safety findings of SC tocilizumab were generally similar to that of IV tocilizumab, both in this clinical program, and historical IV controls. Although not a direct comparison in one study, SAEs/AEs, SAEs/AEs leading to withdrawal, infections, injection site reactions, hypersensitivity, and Grade 1/2 neutropenia occurred more frequently in the SC qw group as compared with the SC q2w group. While limited by cross-study comparisons, the

assessment of the safety profiles of each SC dosing regimen supports the initiation of SC tocilizumab therapy with q2w dosing in patients weighing < 100 kg.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. Efficacy and safety findings in the clinical program for the fixed dose subcutaneous formulation of tocilizumab were consistent with findings from the intravenous tocilizumab experience and did not warrant discussion at an advisory committee meeting.

10. Pediatrics

This submission for the adult RA indication invokes a requirement for a pediatric assessment in polyarticular juvenile idiopathic arthritis (pJIA) patients, as per the Pediatric Research Equity Act (PREA). In this submission, the applicant has provided a request for deferral of studies in pJIA patients 2-17, and a waiver for the 0-2 year old age group, given that pJIA is extremely rare in very young children. Tocilizumab IV is approved for sJIA (since April 2011) and pJIA (since April 2013) in patients 2 years of age and older. The applicant submitted a proposed pediatric study request in December 2011. A pediatric written request was sent to the sponsor in November 2012. The studies included in the pediatric written request are summarized below in Table 4.

Table 2. Pediatric written request (Nov 2012)

Study	Dx	Age (yrs)	N	Dose	Time (wks)	Endpoints
1	sJIA	0-2	10	12 mg/kg IV q4w	12	PK/Safety
2	pJIA	2-17	160 *	< 30kg: 8 or 10mg/kg IV q4w ≥ 30kg: 8 mg/kg IV q4w	64	Long-term safety/tolerability
3	sJIA	2-17	-	SC	14	PK/PD/Safety; Similar C_{min} range
4	pJIA	2-17	-	SC	14	PK/PD/Safety Similar range of exposures

*Subjects already enrolled in randomized, double-blind, placebo controlled efficacy withdrawal trial used for approval of PJIA indication.

The sponsor responded to the pediatric written request on March 2013 with new protocols for the TCZ SC pediatric studies (Table 5) with an agreement that these study reports would be submitted by May 31, 2018.

Table 5. Sponsor proposed pediatric TCZ SC studies (Mar 2013)						
Study Name	**Disease**	**Age (yrs)**	**N**	**TCZ SC Dose**	**Duration (weeks)**	**Endpoints**
WA28118 (Study 3)	sJIA	1-17	48	<30kg: 162mg q10days ≥30kg: 162mg qw	52	PK/PD/Safety -PK @ 14 wks
WA28117 (Study 4)	pJIA	1-17	48	< 30kg: 162mg q3w ≥30kg: 162mg q2w	52	PK/PD/Safety -PK @ 14 wks

The sponsor's proposed pediatric plan was presented to the Pediatric Review Committee (PeRC) on August 28, 2013, and the plan was deemed acceptable.

11. Other Relevant Regulatory Issues

The Applicant conducted the clinical studies using Good Clinical Practices and provided the majority of required financial disclosure information for investigators. The sponsor was unable to obtain financial disclosure from 16 sub-investigators, however these investigators in total randomized a total of 84 subjects in Study WA22762, which does not pose a conflict of interest that would have impacted the overall conclusions of the review. A DSI audit was not requested, as the efficacy data did not appear to be questionable. Further, a total of 333 sites enrolled patients in each of the two pivotal efficacy studies, such that each study site enrolled a small number of patients and, therefore, an audit of even several sites was unlikely to be informative. During review of the submission, no irregularities were found that would raise concern regarding data integrity.

12. Labeling

- **Propietary name –** No change to the proprietary name "Actemra" is proposed.

The main focus of the labeling changes proposed by SEALD and DMEPA centered on constructing the label to minimize any confusion regarding the SC and IV products. To this end, it was recommended that we avoid the abbreviations of SC and IV in the package insert as much as possible. The two routes of administration were discussed separately with respect to safety and efficacy. Comments regarding the patient package insert and instructions for use have been generated by DMEPA and are currently with the Applicant.

- **Physician labeling**

The primary labeling issue with this application pertained to the addition of the data from the tocilizumab SC development program to the package insert for the IV formulation. (b) (4)

when results were consistent with those of the IV dosing regimen, this was stated in the label without unnecessary detail. The Applicant also proposed a change in laboratory monitoring which was supported by data submitted for our review in response to an information request.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

Final labeling has not been completed at the time of this CDTL review, however no major issues of disagreement are anticipated. In addition, because the IV and SC formulations of tocilizumab are under separate BLA numbers, but included within the same label, the newly agreed upon label will need to be submitted to the IV BLA 125276 via a CBE supplement. Once we have agreed upon labeling with the Applicant, we plan to have the Applicant submit a CBE labeling supplement to the IV BLA, and take action on both this application and the CBE supplement simultaneously.

- **Carton and immediate container labels (if problems are noted)**

Final review of carton and container labels is complete; the carton and container labels were found to be acceptable.

- **Patient labeling/Medication guide (if considered or required)**

DMEPA and DRISK are currently reviewing the patient labeling and have submitted comments to the Applicant.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval, with revisions to proposed labeling.

- **Risk Benefit Assessment**

The overall risk benefit assessment supports the approval of tocilizumab for fixed dose subcutaneous administration in patients with RA. The submitted data provided in this application provided adequate evidence that the tocilizumab SC formulation and route of administration is not inferior to the tocilizumab IV formulation and route of administration with respect to efficacy and safety. In addition, the efficacy and safety evaluations support the two dosing regimens. Consistent with the Agency's previous conclusion that the risk-benefit profile of IV tocilizumab is favorable, the data support that SC tocilizumab has a similar risk-benefit profile, and therefore may also be approved. The safety of tocilizumab administered by the subcutaneous route does not show any new or unique safety findings.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

The data in this application do not suggest any new or unexpected safety signals. Tocilizumab IV has a REMS which will need to be updated with the information regarding the SC

formulation and route of administration. The revised REMS will then be submitted to the BLAs for both the IV (125276) and SC (125472) formulations.

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

Post-marketing requirements:
This application triggers PREA. The applicant will be required to conduct a study of SC tocilizumab in pJIA patients ages 2 to 17 years. This study has also been included as part of written request for tocilizumab, as listed in Section 10 above. The Applicant proposed timelines to submit the study reports by May 2018 are acceptable.

Post-marketing commitments:
One microbiology PMC has already been agreed to by the Applicant. The Applicant has agreed that they will determine the (b) (4) volume necessary for (b) (4) and will provide the report by October 30, 2013.

- **Recommended Comments to Applicant**

Not applicable.

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/s/

BANU A KARIMI SHAH
09/30/2013