CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125472Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA 125472 REVIEW AND EVALUATION

Application number:	125472
Supporting document/s:	000
Applicant's letter date:	Dec 21, 2012
CDER stamp date:	Dec 21, 2012
Product:	Tocilizumab
Indication:	Adult patients with moderate to severe active Rheumatoid arthritis
Applicant:	Genentech
Review Division:	Division of Pulmonary, Allergy and Rheumatologic Drug Products
Reviewer:	Asoke Mukherjee, Ph.D
Supervisor/Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Philantha Bowen

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction:

Tocilizumab is a recombinant humanized IgG1k monoclonal antibody that targets the IL-6 receptor. Tocilizumab, administered by the intravenous route, is approved for the treatment of moderate to severe adult rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (SJIA) and polyarticular juvenile idiopathic arthritis (PJIA). The present BLA submission is seeking the approval of a single use, fixed dose (162 mg) subcutaneous dosage form in a pre-filled syringe for self-administration for the treatment of adult RA.

1.2 Brief Discussion of Nonclinical Findings:

The sponsor conducted a complete non-clinical program for Tocilizumab using the intravenous route of administration that was reviewed under BLA 125276. In the pivotal 6-month repeat dose toxicity study of Tocilizumab with cynomolgus monkeys that received dose 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. To bridge toxicity characterized by the intravenous route, the sponsor conducted a 9-week subcutaneous study in cynomolgus monkeys that received a dose of 100 mg/kg/week SC. Tocilizumab did not show any local toxicity at injection sites in cynomolgus monkeys.

The SC dose of 180 mg was found to be bioequivalent to the identical IV dose in the mini-pig model.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg per kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at 10 mg per kg and 50 mg per kg doses (1.25 and 6.25 times the human dose of 8 mg per kg every 2 to 4 weeks based on a mg per kg comparison).
Fertility studies conducted in male and female mice using a murine analogue of tocilizumab showed no impairment of fertility.

1.3 Recommendations:

The sponsor's nonclinical program provides adequate support for the subcutaneous administration of tocilizumab to Adult Subjects with RA. From the non-clinical

perspective, approval of the BLA is recommended. Recommendations for changes to the product label are shown below.

1.3.1 Approvability:

From a nonclinical point of view, the BLA is recommended for approval pending incorporation of recommended changes to the product label.

1.3.2 Additional Non-Clinical Recommendations:

None

1.3.3 Labeling:

Recommended labeling is listed below:

Recommended label (Insertions are noted in bold font and deletions in strikethrough font):

----------INDICATIONS AND USAGE----------
ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of

8.1 Pregnancy

Pregnancy Category C

(b) (4)

(b) (4)

*Pregnancy **Exposure** Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary

Adequate and well-controlled studies with ACTEMRA have not been conducted in pregnant women. In animal reproduction studies, administration of tocilizumab to cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at dose exposures 1.25 times the human dose exposure of 8 mg per kg every 2 to 4 weeks. The incidences of malformations and pregnancy loss in human pregnancies have not been established for ACTEMRA. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were dosed intravenously with tocilizumab (daily doses of 2, 10, or 50 mg per kg from gestation day 20-50) during organogenesis. Although there was no

evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at 10 mg per kg and 50 mg per kg doses (1.25 and 6.25 times the human dose of 8 mg per kg every 2 to 4 weeks based on a mg per kg comparison).

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 per kg intravenously 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.

8.3 Nursing mothers

It is not known whether tocilizumab is present (b) (4) in human milk or if it would be absorbed systemically **in a breastfed infant after oral** ingestion. **IgG is excreted in human milk and therefore it is expected that tocilizumab will be present in human milk**. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

[redacted] (b) (4)

Impairment of Fertility. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab **administered by the intravenous route at a dose of 50 mg/kg every three days** showed no impairment of fertility.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 375823-41-9

Tradename: ACTEMRA™

Generic Name: Tocilizumab

Code Name: RO4877533, MRA

Chemical Name: Recombinant humanized anti-human interleukin 6 receptor (IL-6R) monoclonal antibody

Pharmacological Class: Interleukin 6 receptor antagonist

Molecular Formula/Molecular Weight: 148 kDa

Structure or Biochemical Description:

Generic Name:	Tocilizumab
Code Number:	Drug Substance: RO4877533 Drug Product: Ro 487-7533 (b) (4) (for 200 mg strength) Ro 487-7533 (for 400 mg strength) Ro 487-7533 (for 80 mg strength) Placebo: Ro 487-7533 (matching 200 mg strength)
Chemical Name:	Recombinant humanized anti-human IL-6R monoclonal antibody
Chemical Structure:	H2L2 polypeptide structure consisting of two light chains and two heavy chains held together by disulfide bonds. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. (b) (4)
Empirical Formula:	
Molecular Weight:	Approximately kDa
Description:	Colorless to pale yellow liquid

2.2 Relevant INDs and BLAs:

Table 1. List of BLAs

IND/BLA	Indication	Status	Date approval
BLA 125276	Adult rheumatoid arthritis	Approved	Jan 8, 2010
BLA125276-S 7	Adult Rheumatoid arthritis with structural change	Approved	Jan 4, 2011
BLA 125276, S-10,11	Improvement of physical function in rheumatoid arthritis patients and update of package insert	Approved	April 11, 2011
BLA 125276-S22	Improvement of active systemic juvenile idiopathic arthritis in patients 2 years of age and older	Approved	April 15, 2011

IND/BLA	Indication	Status	Date approval
BLA 125276-S49	Adult rheumatoid arthritis who did not responds to DMARD	Approved	Oct 11, 2012
BLA 125276-S64	Polyarticular juvenile idiopathic arthritis in patients 2 years of age and older	Approved	April 29, 2013

Table 2. List of INDs

IND	Indication	Status	Date submitted
[redacted] (b) (4)			
IND 11972	Adult RA	Active	Aug 29, 2011
[redacted] (b) (4)			

2.3 Drug Formulation:

Dosage form is Pre-filled syringes delivering 162 mg Tocilizumab in 0.9 ml as sterile, preservative free, colorless to slightly yellowish solution. The formulation of the drug product is shown below.

Table P.1-1 [PFS+NSD] Composition of Actemra SC PFS 162 mg/0.9 mL

Ingredient	Nominal Amount/PFS	Concentration	Function	Specifications
Tocilizumab	162 mg	180 mg/mL	Active ingredient	In-house specifications (Section S.4.1 Specification, Drug Substance)
Polysorbate 80	[redacted]			Ph. Eur./USP NF/JP
L-Arginine				Ph. Eur./USP NF/JP
L-Arginine Hydrochloride				Ph. Eur./USP NF/JP
L-Methionine				Ph. Eur./USP NF/JP
L-Histidine				Ph. Eur./USP NF/JP
L-Histidine Hydrochloride Monohydrate				Ph. Eur./JP
[redacted] Water for Injection				Ph. Eur./USP NF/JP

NA=not applicable; [redacted]

[a] pH approximately 6.0.

Comments on Novel Excipients:

There is no inactive ingredient safety issue related to the formulation

Description of device

The primary container closure for Actemra SC includes a clear, [redacted] 1 mL glass barrel with a staked-in 27G ½ in hypodermic needle, which is sealed with a rigid needle shield (RNS) comprised of [redacted] a [redacted] shell and a [redacted] rubber plunger stopper with a [redacted]. A needle safety device is assembled with the PFS. It is not considered part of the primary container closure as it does not directly contact the Drug Product and interacts only with the external surface of the syringe.

2.5 Comments on Impurities/Degradants of Concern:

None

2.6 Proposed Clinical Population and Dosing Regimen:

The SC formulation of Tocilizumab would be used for the treatment of adult patients with moderately to severely active rheumatoid arthritis. The recommended adult SC dose is 162 mg every other week, followed by an increase to every week based upon

clinical response. For patients with body weight over 100 kg, the dose would be 162 mg every week

2.7 Regulatory Background:

Tocilizumab, a monoclonal antibody that targets the IL-6 receptor, is approved for the treatment of moderate to severe adult rheumatoid arthritis, systemic juvenile idiopathic arthritis, and ploy-articular juvenile idiopathic arthritis. Treatment of these indications with Tocilizumab is by the intravenous route.

The subcutaneous route of administration was investigated under INDs 11972, (b) (4) for the treatment of adult RA, (b) (4) In the present BLA, the sponsor has developed a SC formulation of Tocilizumab and is seeking approval for the treatment of rheumatoid arthritis using pre-filled syringes intended for self-administration. The sponsor had several meetings with the FDA regarding the development plan for the SC formulation of Tocilizumab.

A teleconference was held between the sponsor and Agency on Oct 31, 2012 and the sponsor was asked to submit an original BLA (b) (4). In addition, the following response to the sponsor's non-clinic question was sent

Question 6: Roche has conducted a 9-week Monkey SC bridging toxicity study. In the letter dated 9 March 2009, Roche received feedback on the design of this study. Does the Agency agree that this study adequately addresses the Agency's feedback?

FDA Response to Question 6:

Yes, we agree that the 9-week SC bridging study is adequate.

The sponsor has a complete nonclinical program for Tocilizumab using the intravenous route of administration, which includes a 6-month systemic toxicity study in cynomolgus monkeys, an embryofetal development study in cynomolgus monkeys, fertility and post-natal development in mice, and immunotoxicity and a juvenile toxicity study in mice. These non-clinical studies were reviewed under BLA 125276, BLA 125276-s64, IND (b) (4) IND (b) (4) BLA 125276-S49, BLA 125276-S-22, and BLA 125276-S7. In addition, the sponsor submitted two non-clinical subcutaneous studies as listed in the table below. Review of these two non-clinical subcutaneous bridging studies provides non-clinical support for the SC formulation.

Two non-clinical SC bridging and bioequivalency studies are listed in the table below.

Study #	Title	Purpose
1029905	RO4877533 (Actemra): 9-week subcutaneous administration	To identify the local toxicity related to subcutaneous

Study #	Title	Purpose
	toxicity study in the cynomolgus monkey with a 16-week recovery phase	administration of the drug
1026842	RO4877533 (Actemra™, tocilizumab): SC Bioavailability Study of tocilizumab/rHuPH20 Formulations in Göttingen Minipigs	Bioavailability of SC dosage form compared to IV dosage form

Study # 1029905 was reviewed under IND (b) (4) and IND 11972. Study # 1026842 was reviewed for the BLA.125472.

3 Studies Submitted

3.1 Studies Reviewed:

1. RO4877533 (Actemra, tocilizumab): SC bioavailability study of tocilizumab/eHuPH20 formulations in Gottingen minipigs, study # 165.001

2. RO4877533 (Actemra): 9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16 week recovery phase, study # 8025P08 (Review under IND (b) (4); See attachment in the appendices)

3.2 Studies Not Reviewed:

None

3.3 Previous Reviews Referenced:

1. Non-clinical data for Tocilizumab was reviewed for the original BLA 125276 application dated Nov 19, 2007 and additional required non-clinical data was reviewed for the CR response dated July 8, 2009. The original review dated Aug 15, 2008 and CR response review dated Dec 17, 2009 provide an assessment of the sponsor's nonclinical program for Tocilizumab using the intravenous route of administration.

2. To bridge to the subcutaneous route of administration, non-clinical data for the 9-week subcutaneous bridging toxicokinetic study in monkeys (study # 1029905) was reviewed under IND (b) (4) and IND 11972.

4 Pharmacology

No new pharmacology data were submitted. Refer to the review of BLA 125276 dated August 15, 2008.

5 Pharmacokinetics/ADME/Toxicokinetics

Refer to the review of BLA 125276 dated August 15, 2008 for additional information on pharmacokinetics and toxicokinetics.

5.1 PK/ADME

RO4877533 (Actemra, tocilizumab): SC bioavailability study of tocilizumab/eHuPH20 formulations in Gottingen minipigs, study # 165.001

A non-GLP study was conducted on Jan 16, 2008 in female mini-pigs that weighed approximately 9 kg. The objective of the study was to determine bioequivalence between single SC or IV administration. The sponsor also included several formulations containing [redacted] (b) (4)) to increase the bioavailability following SC administration.

The study design is shown below.

The pigs received a single dose of co-formulated test compounds as follows:

- Group 1 (3 minipigs): 20 mg/kg tocilizumab
  IV: 0.444 mL/kg
- Group 2 (5 minipigs): 180 mg tocilizumab
  SC: ca. 1.0 mL/animal
- Group 3 (5 minipigs): 180 mg tocilizumab (2000 U/mL [redacted] (b) (4))
  SC: ca. 1.0 mL/animal
- Group 4 (5 minipigs): 180 mg tocilizumab (6000 U/mL [redacted] (b) (4))
  SC: ca. 1.0 mL/animal
- Group 5 (5 minipigs): 540 mg tocilizumab (6000 U/mL [redacted] (b) (4))
  SC: ca. 3.0 mL/animal

The formulations used in the study are shown below. The PK data from group 1 and 2 animals provides support that the bioavailability of the SC dosage form was comparable to the IV dosage form. Results from groups 3, 4 and 5 are not relevant to the BLA application since these dosage forms included [redacted] (b) (4)

Animal Group		Group 1	Group 2	Group 3	Group 4	Group 5
Administration route		IV	SC	SC	SC	SC
Formulation Batch No.		GIB0001	GIB0001	GIB0002	GIB0003	GIB0003
Composition per 1 mL [2]	RO4877533-000 (Tocilizumab)[1]	180 mg	180 mg	180 mg	180 mg	180 mg
	Polysorbate 80	(b) (4)				
	L-Histidine / L-Histidine-HCl					
	Arginine					
	Methionine					
	(b) (4) [3]					
Dilution with NaCl 0.9% solution for IV injection		1:4				
Dose volume administered		0.444 mL/kg	~1 mL/animal	~1 mL/animal	~1 mL/animal	~3 mL/animal

1) Tocilizumab: Lot T7L01 (nominal concentration)

2) in serile water for injection

3) (b) (4)

Clinical signs and mortality were recorded. The body weight of mini-pigs was recorded at pre-dose, days 7, 14, 21 and 28 after the injection. Blood samples of about 3 ml were collected at each time point from a vein in the neck. Sampling times are shown from the sponsor's table below.

Group 1: Pre-dose and 0.08, 1, 7, 24, 48, 72, 96, 168 hours and 10, 14, 21, and 28 days post-dose.

Groups 2 to 5: Pre-dose and 2, 7, 24, 48, 72, 96, 168 hours and 10, 14, 21 and 28 days post-dose.

Plasma levels of Tocilizumab were determined by an ELISA method with a 0.39 ug/ml limit of detection. Cmax, AUC 0-t, and AUC 0-inf were calculated from the plasma concentration-time curves.

No mortality was observed in the study. Injection site swelling was recorded in group 5 animals. There was no treatment related change in the body weight recorded in the study. The average PK parameters are shown from the sponsor's table below.

Table 3: PK data

Parameter	Unit	Group 2 180 mg tocilizumab SC - -	Group 3 180 mg tocilizumab SC 2000 U (b) (4)	Group 4 180 mg tocilizumab SC 6000 U (b) (4)	Group 5 540 mg tocilizumab SC 18000 U (b) (4) (6000 U/mL)
AUC(0-inf)	[(µg·h)/mL]	69300	75800	67700	166000
AUC(rest, tlast-inf)	[%]	16.4	17.0	14.9	12.9
AUC(0-672h)	[(µg·h)/mL]	57800	62500	57200	141000
Cmax	[µg/mL]	190	213	219	715
tmax	[h]	48	24	24	20.6
t1/2	[h]	262	268	246	260
MRT(tot)	[h]	371	377	353	316
CL/F	[mL/min]	0.0449	0.0388	0.043	0.0562
F**	[%]	83.5	98.4	88.3	72.6

** : calculated by Excel according to equation [2] (see Section 6.2 *Methods*)

Above data indicated that Tocilizumab given by a single SC injection was bioequivalent to a comparable IV dose. The drug was absorbed from the injection site slowly based upon a mean Tmax of 48 hours and there were no treatment related clinical signs at the site of injection.

6 General Toxicology

Refer to the review of BLA 125276 dated August 15, 2008 for additional information on IV toxicology studies conducted with Tocilizumab.

To bridge to the subcutaneous route of administration, a 9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16-week recovery phase (study # 1029905) was reviewed under IND (b) (4) and IND 11972 (attached in appendices).

7 Genetic Toxicology

Genetic toxicity studies are not required for biological products.

8 Carcinogenicity

A carcinogenicity waiver request was reviewed under BLA 125276. Refer to the review of BLA 125276 dated August 15, 2008 for additional information.

9 Reproductive and Developmental Toxicology

Refer to the review of BLA 125276 dated dated August 15, 2008 and the review of the Complete Response dated December 17, 2009 for additional information

10 Special Toxicology Studies

Refer to the review of BLA 125276 dated August 15, 2008 for additional information.

11 Integrated Summary and Safety Evaluation:

Tocilizumab (Actemra) is a monoclonal antibody that targets the IL-6 receptor and is an antagonist to IL-6 soluble and membrane bound receptors. It was approved for administration by the intravenous route in the treatment of RA, pJIA and SJIA at maximum dose of 8 mg/kg/IV every 4 weeks. The maximum dose is 12 mg/kg IV every 2 weeks in pediatric patients with SJIA. The present BLA was submitted to obtain approval of a subcutaneous dosage form in pre-filled syringe at 162 mg to be given every 1 or 2 weeks to RA patients. The sponsor has a complete nonclinical program for Tocilizumab administered by the intravenous route. The sponsor submitted two nonclinical studies to bridge over to the subcutaneous route of administration.

Clinical PK data in human subjects that received a SC dose at 162 mg in study NP22623 showed Cmax of 10.7 ug/ml, Tmax of 72 hr, $AUC_{0\text{-}inf}$ of 1253 ug.hr/ml and $T_{1/2}$ of 43 hours on day 71.

The non-clinical data for the application were supported by the previous BLA 125276. In the pivotal 6-month repeat dose toxicity study of Tocilizumab with cynomolgus monkeys that received dose 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.

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 SC dose of 180 mg was found to be bioequivalent to the identical IV dose in the mini-pig model.

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.

The margin of safety for the proposed clinical dose at 162 mg/SC q 2week (2.7 mg/kg) clinical dose was 37 on the basis of mg/kg doses when compared to the NOEL at 100 mg/kg/week SC in cynomolgus monkeys. Based on the absence of toxicity findings and large margin of safety, it is recommended that the BLA be approved from the non-clinical perspective.

A labeling review that includes labeling recommendations is provided below. In response to the recommendation from SEALD regarding the pending Pregnancy and Lactation Labeling Rule, a consultation to the Maternal Health Team (MHT) was sent on July 25, 2013 for revisions to Sections 8.1 and 8.3 of the draft label. The MHT made revisions to Sections 8.1 and 8.3 of the product label (See Review from Dr. Ceresa dated August 23, 2013).

Labeling Review:

The sponsor has submitted proposed labeling in general conformance with 21 CFR Parts 201, 314 and 601 Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products and with Guidance for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices (January 24, 2006). The recommended nonclinical changes to product labeling are 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).

INDICATIONS AND USAGE

Sponsor's Proposed Labeling: (b) (4) (b) (4)

Evaluation: The sponsor's proposed label for indications and usage was approved for the supplemental BLA 125276-S64 dated April 29, 2013

Recommend Labeling: ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist

8.1 Pregnancy

Sponsor's Proposed Labeling:

8.1 Pregnancy

(b) (4) **Pregnancy Category C.** (b) (4)

[redacted]

Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Evaluation: In response to the recommendation from SEALD regarding the pending Pregnancy and Lactation Labeling Rule, a consultation to the Maternal Health Team (MHT) was sent on July 25, 2013 for revisions to Sections 8.1 and 8.3. of the draft label. The MHT made revisions to Sections 8.1 and 8.3 of the product label on August 23, 2013.

Recommend Labeling:

Pregnancy Category C

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary
Adequate and well-controlled studies with ACTEMRA have not been conducted in pregnant women. In animal reproduction studies, administration of tocilizumab to cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at dose exposures 1.25 times the human dose exposure of 8 mg per kg every 2 to 4 weeks. The incidence of malformations and pregnancy loss in human pregnancies has not been established for ACTEMRA. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data
An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were dosed intravenously with tocilizumab (daily doses of 2, 10, or 50 mg per kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at 10 mg per kg and 50 mg per kg doses (1.25 and 6.25 times the human dose of 8 mg per kg every 2 to 4 weeks based on a mg per kg comparison).

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 per kg intravenously 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.

8.3 Nursing Mothers

Sponsor's Proposed Labeling:

8.3 Nursing Mothers

It is not known whether tocilizumab is excreted in human milk (b) (4)

Evaluation: See above under Section 8.1.

Recommend Labeling:

It is not known whether tocilizumab is present in human milk or if it would be absorbed systemically after ingestion. IgG is excreted in human milk and therefore it is expected that tocilizumab will be present in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sponsor's Proposed Labeling:

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

Evaluation: No change to the proposed label is recommended

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's Proposed Labeling:

Carcinogenesis. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

(b) (4)

Impairment of Fertility. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab (b) (4).

Evaluation: For the fertility study conducted with male and female mice, (b) (4)

Recommend Labeling:

Carcinogenesis. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

Impairment of Fertility. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab administered by the intravenous route at a dose of 50 mg/kg every three days showed no impairment of fertility.

12 Appendix/Attachments

Appendix 1: RO4877533 (Actemra): 9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16 week recovery phase (study # 8025P08) reviewed under IND (b) (4) dated December 13, 2011. The review is attached as follows:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	(b) (4) IND 11972
Supporting document/s:	000 for IND (b) (4) and 966 for IND 11972
Sponsor's letter date:	(b) (4) for IND (b) (4) and April 16, 2009 For IND 11972
CDER stamp date:	(b) (4) for IND (b) (4) and April 17, 2009
Product:	Tocilizumab
Indication:	(b) (4)
Sponsor:	Roche Inc
Review Division:	Division of Pulmonary, Allergy and Rheumatology Drug products, HFD-570
Reviewer:	Asoke Mukherjee, Ph.D
Supervisor/Team Leader:	Molly Topper, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Philantha Bowen

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1 Executive Summary

1.1 Recommendations:

The applicant proposes to conduct the clinical study at 162 mg SC/week for 48 weeks as a randomized blinded study and thereafter, it will continue as an open label study for another 48 weeks. Actemra (tocilizumab) is already under investigation under two Roche sponsored Phase 3 protocols in RA patients at 162 mg/week/SC under IND (b) (4) From the Pharmacology/Toxicology point of view, the proposed protocol is safe.

1.1.1 Clinical Study (ies) Safe to Proceed: Yes

1.2 Brief Discussion of Nonclinical Findings:

A 9-week subcutaneous toxicity study in cynomolgus monkeys with a 16-week recovery was conducted at 100 mg/kg/week/SC. The toxicity study did not show any treatment related changes in clinical signs, body weights, clinical pathology and organ weights. However, minimal to slight fibrosis of the kidneys and degeneration of the ovary were observed at the 100 mg/kg dose. The finding in kidneys was not considered to be treatment related because a 6-month toxicity data in cynomolgus monkeys up to 100 mg/kg/week/IV (study # Tox-02-0169, given by slow IV infusion for 10 mins, once per week) did not show the lesion that was observed in the 9-week SC toxicity study despite comparable plasma concentrations of tocilizumab in both studies. The plasma trough levels of tocilizumab at 100 mg/kg/IV was 1935 ± 340 in male and 1936 ± 379 in female monkeys. The plasma trough levels of tocilizumab after SC administration was 2580 ± 464 in male and 2230 ± 490 ug/ml. Therefore, it was concluded that the treatment of cynomolgus monkeys at 100 mg/kg/SC dose for 9 weeks did not show any treatment related toxicity and NOEL was 100 mg/kg/SC. The dose studied was 37 times higher than the proposed clinical dose at 162 mg/week/SC on mg/kg basis.

2 Drug Information

2.1 Drug

Actemra (tocilizumab)

2.1.1 CAS Registry Number (Optional):

375823-41-9

2.1.2 Generic Name: Tocilizumab

2.1.3 Code Name: RO4877533

2.1.4 Chemical Name: Recombinant humanized interleukin 6 (IL-6) receptor monoclonal antibody

2.1.5 Molecular Formula/Molecular Weight: 148 kDa

2.1.6 Structure

Generic Name:	Tocilizumab	
Code Number:	Drug Substance:	RO4877533
	Drug Product:	Ro 487-7533 (b) (4) (for 200 mg strength)
		Ro 487-7533 (for 400 mg strength)
		Ro 487-7533 (for 80 mg strength)
	Placebo:	Ro 487-7533 (matching 200 mg strength)
Chemical Name:	Recombinant humanized anti-human IL-6R monoclonal antibody	
Chemical Structure:	H2L2 polypeptide structure consisting of two light chains and two heavy chains held together by disulfide bonds. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively.	
	(b) (4)	
Empirical Formula:		
Molecular Weight:	Approximately (b) (4) kDa	
Description:	Colorless to pale yellow liquid	

2.1.7 Pharmacologic class:

Monoclonal antibody to IL-6 receptor

2.2 Relevant IND/s, NDA/s, and DMF/s

IND#	Status	Division	Indication	Status Date	Sponsor
(b) (4)					
11972	Active	DAARP	Treatment of adult onset rheumatoid arthritis	11/04/2004	Hoffman-La Roche
(b) (4)					
BLA125276	Approved	DAARP	Rheumatoid arthritis	Jan 8, 2010	Hoffman La Roche

2.3 Clinical Formulation:

The clinical formulation contains 180 mg of tocilizumab per ml in ready to inject syringe for SC injections. The formulation does not contain a preservative. The inactive ingredients are polysorbate 80, L-arginine hydrochloride, L-methionine and L-histidine. These inactive ingredients are used in FDA approved products at concentrations equal or higher than listed in the formulation and there is no inactive ingredient safety issue to the product. The placebo contains the vehicle without tocilizumab. The formulation per ml is shown below.

Table 1. Clinical formulation for subcutaneous administration

Ingredient	Actemra, SC, 180 mg/ml	Function
Tocilizumab	180 mg/ml	Active ingredient
(b) (4) buffer	Histidine, (b) (4)	(b) (4) buffer

Polysorbate 80	(b) (4)	(b) (4)
L-arginine HCL		
L-methionine		
(b) (4) water for injection		

2.4 Proposed Clinical Population and Dosing Regimen:

Clinical protocol # WA27788A submitted to the IND is briefly discussed below.

A. Title:

A PHASE II/III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB VERSUS PLACEBO IN PATIENTS WITH SYSTEMIC SCLEROSIS

This is a Phase 2/ 3 protocol for a 48-week multi-center study with open-label extension for another 48 weeks. Approximately 86 patients will be enrolled in the two-arm study. 43 patients will receive treatment with tocilizumab at 162 mg/week/SC and another 43 patients will receive treatment with placebo. Patients will be treated at 162 mg/week/SC doses or placebo for 48 weeks in blinded study. Safety, efficacy and kinetic data will be gathered.

Male and female adult patients 18 years and older with SSC (systemic sclerosis) will be enrolled. Some of the inclusion criteria related to the Pharmacology/Toxicology review are shown below.

1. Females of childbearing potential may participate in the trial only if the patient has a negative pregnancy test at screening and the base line visit.

Some of the exclusion criteria are shown below.

1. Presence of primary or secondary immunodeficiency syndrome

2. Evidence of malignancy within past 5 years

3. Patients with reproductive potential not willing to use an effective method of contraception, such as oral, injected, or implanted hormonal methods of contraception, intrauterine device or intrauterine system, condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, suppository, male sterilization, or true abstinence

2.5 Regulatory Background

2.5.1 Previous Clinical Experience:

Tocilizumab is approved for the treatment of RA and JRA by IV route of administration The maximum recommended dose for the adult patients is 8 mg/kg/IV/4 week and the maximum recommended dose for JRA patients is 8-12 mg/kg/IV/2 week.

3 Studies Submitted

Report # 1029905 “9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16-week recovery phase,” this study report was submitted to IND 11972 (SDN 966), date of submission of the study report was 04/16/2009. This study report was cross-referenced for the IND (b) (4) submitted on (b) (4). .

Repeat-dose toxicity

Study title: 9-week subcutaneous administration toxicity study in the cynomolgus monkey with a 16-week recovery phase.

Key study findings: No treatment related changes in the food consumption, body weight, clinical pathology, organ weight, macroscopic and histopathology were observed. NOAEL was 100 mg/kg/week/SC.

Study no.: **1029905**

Conducting laboratory and location:

(b) (4)

Date of study initiation: April 8, 2008

GLP compliance: Yes

QA report: yes (x) no ( )

Drug, lot # and % purity:

RO4877533 (Actemra), Batch S8B01, 99.6% pure, 180 mg/ml, the liquid, ready to use formulation containing 180 mg/ml of the drug substance was used. The control vehicle was saline.

Methods

Study design

Doses:

Table 2. Study Design

Group	Treatment	Dose, mg/kg/week/SC	#, Main study, Male	#, Main study, Female	#, Recovery, Male	#, Recovery, Female
1	Control	vehicle	3	3	2	2
2	Tocilizumab	100 mg/kg	3	3	2	2

Species/strain: cynomolgus monkeys

Number/sex/group or time point (main study): see study design above

Route, formulation, volume, and infusion rate: SC, ready to use formulation containing clear solution of tocilizumab (applicant did not provide formulation) once weekly at 0.55 ml/kg volume. The vehicle group received commercial sodium chloride for injection.

Satellite groups used for recovery:
2/group/sex was allotted to recovery

Age: Approximately 3- 4 years of age

Weight: 3.0 to 3.8 kg for male and 3.6 to 5.2 kg for female monkeys

Observations and times:

Mortality: Mortality was observed twice daily

Clinical signs: General conditions, feces, fur and behavior were observed once a day. The testicular size was examined by ultrasound techniques before dosing and at the end of dosing period.

Body weights: The body weight was recorded three times before dosing, once a week during dosing and during the recovery period. The body weight was also recorded at the time of necropsy.

Food consumption: Food consumption was not recorded.

Toxicokinetics:

Blood samples were collected (1 ml) on days 1 and 50 (8 week) of dosing at predose, 24, 72 and 168 hours post dose. Predose samples were also taken on weeks 3 and 5 from all animals

Blood samples from the recovery period were taken every two weeks after the last dose on days 71, 85, 99, 113, 127, 141, 155 and 169. Following PK parameters were determined.

T_{max}, C_{max}, AUC, C_{ave}

Plasma levels of tocilizumab were determined by ELISA

Antibody to tocilizumab was determined from all animals on day 1 at predose and day 50 at 168 hours post dose. Days 71, 85, 99, 113, 127, 141, 155 and 169 from group 2 recovery animals. Antibody to tocilizumab was also determined on day 169 from the control animals.

Hematology, coagulation and blood chemistry:

3 ml of blood samples were taken for standard hematology parameters once in predose and on week 9 of the dosing and at the end of recovery period. Blood neutrophil counts were also monitored on weeks 1 and 8 from the samples collected for TK analysis. A complete clinical chemistry parameter was determined from the blood samples collected for hematological examinations. In addition, liver enzymes were assayed at 24 and 72 hours after the first dose.

Urinalysis: Urine samples were collected for 2 hours from fasted animals at predose, in week 9 and at the end of recovery period. Standard urine chemistry parameters were evaluated.

Gross pathology: Animals were sacrificed by exsanguination under anesthesia with Ketamin and Nembutal injections.

Macroscopic changes in the systemic organs were recorded.

Organ weights: The organ weight of following organs was recorded at necropsy:

Spleen, adrenals, kidneys, liver, ovaries, testes and epididymides

The organ weight data was presented as absolute weight, % of body weight and % of brain weight.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

A complete battery of tissues (list provided in the submission), any gross lesion and injection sites were fixed in 10% formalin. However, bone marrow smears were fixed in methanol, and testes, epididymides were fixed in modified Davidson's fluid. Eyes and optic nerve was fixed in Davidson's fixative. Histopathology of tissues from main and recovery groups were conducted for all animals in the control and treated groups.

Tissues were embedded in paraffin, sectioned at 5 uM, stained with hematoxylin and eosin for histopathological examinations. Tissues from the liver were stained with PAS stain.

Myeloid to erythroid ratio was determined following staining bone marrow cells with Wright stain.

Results

Mortality:

No unscheduled deaths were observed in the study.

Clinical signs:

No treatment related clinical signs were observed.

Body weights: No treatment related changes in the body weight were observed.

Testicular size:

There was no treatment related effect on the testicular size.

Hematology: No treatment related change in the hematology and coagulation parameter was observed.

Clinical chemistry:

No treatment related change in the clinical chemistry parameters was observed.

Urinalysis: There was no treatment related changes in the urine analysis.

Gross pathology:

There was no treatment related gross change in the visceral organs and at the injection sites.

Organ weights:

No treatment related change in the organ weights was observed. Left kidneys in the male animals showed an increase in the absolute weight from 7.7 g in the control to 10.4 g in the treated group ($P< 0.05$). However, the change was not considered as treatment related due to absence of a similar finding in the right kidney. Also, female animals did not show any treatment related change.

Histopathology:

Table 3. Histopathology

Lesion	Control Male, n=3	100 mg/kg, male, n=3	Control, Female, n=3	100 mg/kg, Female, n=3
Injection site, inflammatory cell foci	1	3	3	2
Min	1	2	2	1
Slight	0	1	1	1
Recovery, n= 2	0	0	1	1
min	0	0	1	1
Kidneys, fibrosis	0	1	0	1
min	0	0	0	1

Lesion	Control Male, n=3	100 mg/kg, male, n=3	Control, Female, n=3	100 mg/kg, Female, n=3
Slight	0	1	0	0
Recovery, n=2	0	0	0	0
Ovaries, degeneration	NA	NA	0	1
Moderate	NA	NA	0	1
Recovery, n=2	NA	NA	0	0

NA = not applicable

Subcutaneous injections did not show any treatment related histopathological change in the Injection site and no macroscopic change at the site of injection due to the treatment with tocilizumab was observed. No treatment related change was observed in the lymphoid system due to the route specific delivery of the drug.

Fibrosis (minimum to slight) in the kidneys was observed at 100 mg/kg/week/SC that was not present in the recovery animals. The applicant did not specify in the histopathology report if these changes were unilateral or bilateral in the organ.

Fibrosis of the kidney in male and female monkeys was considered to be incidental due to lack of a similar finding in a 6-month intravenous toxicity study in cynomolgus monkeys up to 100 mg/kg.

One out of 3 female monkeys in the treated group also showed moderate ovarian degeneration at 100 mg/kg/week/SC. However, there were no ovarian lesions observed in the cynomolgus monkeys following intravenous treatment at 100 mg/kg/week for 6 months that was reviewed under BLA 125276. Therefore, lesions in the reproductive organs were incidental and not related to the subcutaneous injections of tocilizumab for 9 weeks.

The comparison of tocilizumab exposure between SC and IV routes of administration could not be made due to absence of the exposure data from the 6-month intravenous toxicity study in the monkeys. However, The average plasma concentration data in 9-week SC treatment at 100 mg/kg/week and 6-month IV treatment at 100 mg/kg/week showed plasma concentrations of 2405 (male 2580 ± 464, female 2230 ± 490) and 1936 ug/ml (male 1936 ± 379, female 1935 ± 340), respectively. The six-month IV toxicity data in cynomolgus monkeys showed no effect on the body weight, food consumption, clinical chemistry and hematology similar to that observed in the SC route of administration. The IV dose for 6-month showed slight granuloma of the liver and slight degenerative change in the skeletal muscle that were not observed in the 9-week SC route of administration despite a comparable plasma level of tocilizumab. Based on the absence of histopathological changes in the kidney, testes, ovary, injection sites,

lymph nodes at comparable plasma levels of the drug, in the 6-month IV toxicity study, it was concluded that the SC route of administration did not induce any route specific treatment related toxicity in cynomolgus monkeys. Therefore, NOAEL of the study was 100 mg/kg/week/SC.

Toxicokinetics:

No gender differences in the PK were noted in the study. The predose and 168 hour post dose concentrations showed accumulation of the drug over the period of study in the plasma. It cannot be confirmed if a steady state level in the plasma was reached based on the average trough concentrations on days 1, 15, 29, 50 that showed increasing trough levels. However, comparison of average plasma levels between the SC and IV route of administration suggest that the plasma level of the drug after SC doses were comparable to the level achieved at the steady state after IV administrations. The recovery data showed the clearance of the drug at the end of recovery was almost complete and about 0.5 to 1% of the drug was detected in the plasma compared to that observed as the trough level after the last injection.

Trough levels of the drug in male and female monkeys are shown below.

Table 4. Average trough levels (ug/ml) of tocilizumab after SC injections

Day	C trough (ug/ml)	
	Male, n=5	Female, n=5
1	857 ± 137	749 ± 142
15	1160 ± 232	1130 ± 88
29	1780 ± 178	1600 ± 464
50	2580 ± 464	2230 ± 490
169 (recovery), n=2	26	10.5

Table 5. PK parameters of SC tocilizumab at 100 mg/SC on day 1 and day 50 in cynomolgus monkeys

	Tmax, hr		Cmax, ug/ml		AUC, ug.hr/ml	
Day	Male	Female	Male	Female	Male	Female
1	72	72	1180	1150	160000	142000
50	24	24	3410	3140	507000	448000

The average male and female combined Tmax, Cmax and AUC 0-168 hours was 24 hours, 3280 ug/ml and 478000 ug.h/ml, respectively . No anti-drug antibody was detected.

Conclusion of 9-week subcutaneous toxicity study in monkeys:

Cynomolgus monkeys were treated at 100 mg/kg/week/SC for 9 weeks and satellite groups were observed for 16-week recovery. No mortality was observed and no changes in the body weight, food consumption, clinical chemistry and hematology were observed following SC administration of tocilizumab. Histopathology data in the SC toxicity study showed fibrosis of the kidneys. However, the effect was considered to be spontaneous in these monkeys rather than the treatment related change because the data from a 6-month toxicity study at similar plasma concentration did not confirm the histological finding. Moderate ovarian degeneration was observed in one out of 3 monkeys. However, it was considered as an incidental finding because this finding was not confirmed in the 6-month IV toxicity study in 100 mg/kg dose. Based on the data, it was concluded that the NOAEL for toxicity was 100 mg/kg/SC for 9 weeks. Bioavailability of SC injection to the IV dose could not be determined from the plasma exposure data because the exposure to IV doses in the 6-month toxicity study was not determined. However, data from a previous study showed plasma bioavailability after SC injections compared to IV dose at 5 mg/kg single dose was about 72% (study # ADM04-0014, BLA 125276).

3.3 Previous Reviews Referenced:

Pharmacology and toxicology data reviewed for Tocilizumab via the IV route can be obtained from the review of original BLA 125276 submitted on Nov 19, 2007 and the CR response to the submission dated July 8 and Nov 4, 2009.

4 Integrated Summary and Safety Evaluation

Tocilizumab will be investigated for the treatment of systemic sclerosis at 162 mg/SC/week a total of 96 weeks in Phase 2/3 studies in adult male and female patients. The clinical safety and efficacy of tocilizumab and nonclinical toxicity have been already reviewed for the approval of BLA 125276 for rheumatoid arthritis at 8 mg/kg/4 weeks/IV doses and at 8-12 mg/kg/2- week/IV in JRA patients. The subcutaneous route of administration is further under investigation for the treatment of RA at 162 mg/SC/week and 162 mg/2 week/SC in Phase 3 studies # MRA229JP, WA22762 and NA 25220.

The applicant conducted a 9-week subcutaneous bridging study in cynomolgus monkeys at 100 mg/kg/week for the assessment of safety of the SC route of administration. Data from the SC study did not show any treatment related effect on clinical signs, body weight, clinical pathology, macroscopic change, organ weight in male and female monkeys. Injection site irritation was also not observed after SC injections. Male and female monkeys at 100 mg/kg/week showed fibrosis of kidneys of minimum to slight severity. However, the change was considered to be incidental when data from 6-month toxicity following IV administration in cynomolgus monkeys were compared. The six-month IV toxicity study showed a slight granulomoutas change in the liver and slight skeletal muscle degeneration at 10 and 100 mg/kg/IV doses. However, there was no effects of tocilizumab observed in the kidneys. Degenerative change in the ovary was observed in the SC toxicity study. However, a similar change was not observed in the 6-month toxicity study following IV administration of tocilizumab at 100 mg/kg. The average plasma trough concentration of the drug by IV and SC route of administration at 100 mg/kg/week was 1930 and 2405 ug/ml, respectively, Although the SC trough levels were higher than that for the IV route, margin of errors for both set of data overlapped. Comparing the toxicity and kinetic data between IV and SC doses, it was concluded that the fibrosis of kidneys and degenerative changes in the ovaries due to SC injections of tocilizumab were incidental. Based on the data, it was concluded that tocilizumab did not show any toxicity in cynomolgus monkeys when injected at 100 mg/kg/Sc Q 1 week for 9 weeks.

The NOAEL was 100 mg/kg/week/SC. The margin of safety at 100 mg/kg/week/SC was 37 times to that proposed for the clinical study based on mg/kg doses. The clinical exposure data by SC route is not available for comparison of margin of safety by dose and exposure when given by SC route. Therefore, from non-clinical Pharmacology/Toxicology perspectives, the IND is safe to proceed at the proposed dose.

Table 6. Margin of safety from the animal doses tested is shown below:

Human	Monkey	Monkey : Human
162 mg/kg/week/SC, 2.7 mg/kg	100 mg/kg/week/SC	37

Recommendation:

The protocol is safe to proceed from non-clinical point of view based on the 37 times margin of safety in the human and previous human experience

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/s/

ASOKE MUKHERJEE
12/13/2011

MOLLY E TOPPER
12/13/2011

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/s/

ASOKE MUKHERJEE
09/09/2013

TIMOTHY W ROBISON
09/09/2013
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA 125472

BLA Number: 125472 **Applicant: Roche** **Stamp Date: Dec 21, 2012**

Drug Name: Tocilizumab **BLA Type: SC injection via Pre-filled syringe for rheumatoid arthritis**

On **initial** overview of the BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		The sponsor submitted a 9-week SC bridging toxicity study reports in cynomolgus monkeys and single dose PK study in mini-pigs for comparison to approved IV Tocilizumab BLA 125276 in support of safety and bioavailability to SC dosing
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		The sponsor referenced approved BLA 125276 with respect to non-clinical data
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		Bioavailability study of SC formulation to IV formulation in mini-pigs was non-GLP. However, it would be acceptable because the SC toxicity study in cynomolgus monkey was conducted according to GLP as a bridging study to approved IV route

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR BLA 125472

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		The proposed label is similar to approved indications for BLA 125276
10	Have any impurity – etc. issues been addressed?		x	Will consult with the Quality Reviewer regarding potential impurity issues.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

None

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/s/

ASOKE MUKHERJEE
01/23/2013

TIMOTHY W ROBISON
01/23/2013
I concur