CLINICAL PHARMACOLOGY REVIEW

BLA	125118
Submission Date	9/30/2016
Brand Name	Orencia
Generic Name	Abatacept
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Team Leader	Jingyu Yu, Ph.D.
Clinical Pharmacology Team Leader	Anshu Marathe, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	BMS
Submission Type; Code	pediatric supplement
Formulation; Strength(s)	PFS
Indication	PJIA
Dosage Regimen	Weight based dosing, 10 to< 25 kg, 50 mg QW; 25 to <50 kg, 87.5mg QW; ⩾50 kg, 125 mg QW

This is an amendment for the clinical pharmacology review (DARRTS date 03/08/2017) for BLA 125118, and review for the sponsor's response to IR on 03/24/2017.

Executive Summary:

The sponsor was seeking approval in patients 6 years and above, therefore, the PK data from 2-5 yr-old cohort was not included in the initial population PK-ER report. An information request (IR) was sent to the sponsor for sensitivity analysis, to include PK data in patients 2-5-yr-old in the population PK analysis. The information request (IR) was made to confirm that the label statement based on population PK analysis is valid for PJIA patients 2-17 years old: "*population pharmacokinetic analyses for subcutaneous abatacept in JIA patients revealed that there was a trend toward higher clearance of*

abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance". At the time of the primary clinical pharmacology review (DARRT date 03/08/2017), the IR was pending.

The sponsor submitted the response to IR on 03/24/2017. 129 samples from 32 patients with JIA aged 2 to 5 years from Study IM101301 were added to the PK dataset. The sensitivity analyses to include data in 2-5 yr patients demonstrate similar PK parameters as the original analysis. A rigorous analysis assessing of the covariate effects on abatacept exposure was performed using population PK methodology. The reviewer was able to confirm the applicant's parameter estimates by rerunning the model. Residual diagnostics based on the sponsor's analyses showed that the model fitted the data reasonably well for abatacept serum concentrations greater than 0.1 μg/mL.

Overall, the analysis, and the corresponding conclusions and interpretations, presented by the sponsor are reasonable. Label statement "Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in JIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance" is valid for PJIA patients 2-17 years of age.

Summary of BMS IR sent on 03/24/2017:

1. What are the covariates contributing to the inter-subject PK variability of abatacept based on population PK analyses? Is dose adjustment warranted with respect to these covariates?

The impact of covariates on abatacept PK was assessed in the updated analyses. As seen in the previous analyses, the clearance of abatacept increased with increasing body weight and the body weight effect on PK was the only statistically significant covariate considered clinically relevant (Figure 1). After taking into account body weight effect, there was no additional effect of age on the clearance of abatacept. No dose adjustment was recommended for with respect to any of the other covariates.

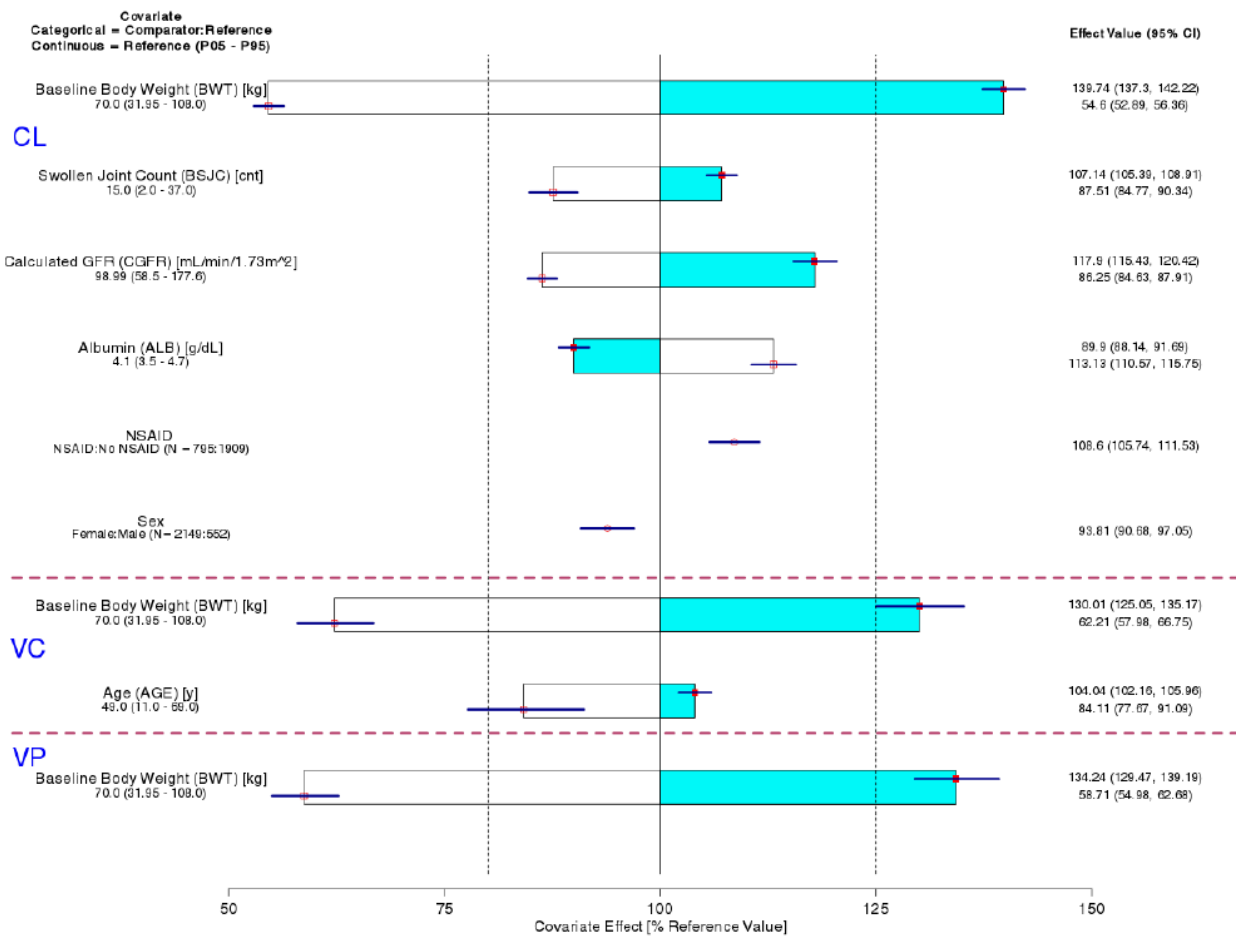

Figure 1. Impact of covariates on PK parameters displayed as ratio- or percentage with 90% CI comparing to a reference patient (updated analysis including patients 2-5 yrs old)
(Source: Figure 1, IR response on Mar 24, 2017)

2. Detailed Labeling Recommendations

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Juvenile Idiopathic Arthritis - Subcutaneous Administration

(b) (4)

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Consistent with the intravenous data, population pharmacokinetic analyses for subcutaneous abatacept in JIA patients revealed that there was a trend toward higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect apparent clearance. Concomitant medication, such as methotrexate, corticosteroids, and NSAIDs, did not influence abatacept apparent clearance.

APPEARS THIS WAY ON ORIGINAL

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/s/

JIANMENG CHEN
03/29/2017

JINGYU YU
03/29/2017

ANSHU MARATHE
03/29/2017