CLINICAL PHARMACOLOGY REVIEW

sBLA	125118/211
Submission Date	9/30/2016
Brand Name	Orencia
Generic Name	Abatacept
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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

1. Executive Summary

1.1 Recommendations

From the viewpoint of the Office of Clinical Pharmacology, the application is acceptable for approval. The weekly weight-tiered SC abatacept dosing regimen is appropriate for pediatric JIA patients 2-17 years of age. In addition, the clinical pharmacology information provided in the final study report IM101301 is acceptable for the fulfillment of the written request (issued Sep 2013, Amendment 1 in Aug 2015).

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Background

BMS has submitted the supplement 211 to BLA125118 to support the use of SC abatacept for the following proposed indication that is identical to that of the approved indication for IV abatacept in JIA: "*ORENCIA is indicated for reducing signs and symptoms in* (b) (4) *years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).*"Abatacept is a fully human, recombinant, soluble fusion protein consisting of the extracellular domain of human CTLA4 and a fragment of the Fc region of human IgG1. Orencia® (abatacept) was approved for IV use for the treatment of adults with RA and children with active JIA in 2005 and 2008, respectively. The SC formulation of abatacept was approved for the treatment of adults with RA in 2011.

As agreed by the Division and stated in the written request, the efficacy of SC abatacept was extrapolated from the IV abatacept JIA data based on PK bridging. Steady state trough concentration (Cminss) is considered the most relevant PK parameter for efficacy in RA and JIA, and Cminss above 10 mcg/mL is associated with near maximal efficacy based on E-R analysis. Per the written request, Cminss at Day 113 was determined to be the primary PK endpoint to support efficacy extrapolation.

The proposed indication is supported by the Phase 3 Study IM101301. IM101301 is an open-label study that evaluated the pharmacokinetics (PK), safety, efficacy, and immunogenicity of a weekly weight-tiered SC abatacept dosing regimen in subjects 2-17 yrs old with JIA. The sponsor also proposed that this submission would fulfil the written request (issued Sep 2013, Amendment 1 in Aug 2015), and requested for exclusivity determination.

The proposed dose of SC abatacept for patients 6 to 17 years of age is 50 mg (10-<25kg), 87.5 mg (25-<50 kg) or 125 mg (≥50 kg) QW. Although study IM101301 included a cohort of patients 2-5 years old, the sponsor was not seeking approval for patients 2 to 5 years old in this application. Upon medical review team's request, the clinical pharmacology review evaluated whether patients 2-5 years old could achieve the desired therapeutic target Cminss of 10mcg/mL and achieve comparable exposure as patients 6-17 years old, with the weekly weight tiered SC abatacept dosing regimen.

Summary of clinical pharmacology findings
The major findings for this Clinical Pharmacology review are as follows:

- A weekly weight-tiered SC abatacept dosing regimen achieved the desired therapeutic target steady state trough concentrations (Cminss ≥10 mcg/mL) in 149 out of 150 evaluable PK subjects (2-17 yrs old) at Day 113. Therefore, the efficacy of SC abatacept in PJIA could be extrapolated from IV abatacept efficacy in PJIA based on higher steady state trough concentrations.
- Comparable steady state trough concentrations across weight tiers were achieved by Day 85 following the weekly body-weight–tiered subcutaneous dosing regimen in JIA patients 2-17 years old (Table 1).

Table 1. Observed steady state Cmin of abatacept in different weight groups

	Pediatric (6 -17 yrs)	**Pediatric (2-17 yrs, 10 to <25kg)**	**Pediatric (2-17 yrs, 25 to <50 kg)**	**Pediatric (2-17 yrs, ≥ 50 kg)**
Route	IV	SC	SC	SC
Dose (mg)	<75kg, 10 mg/kg; ≥75 kg, adult dose W0, W2, W4, Q4W thereafter	50 mg QW	87.5 mg QW	125 mg QW
Day 85				
N	N/A	42	63	65
Cminss (mcg/mL) mean (range)	11.9* (0.15-44.6)	42.4 (8.1-83.4)	44.9 (13.3-80.8)	39.3 (7.4-97.0)
Day 113				
N	N/A	34	61	55
Cminss (mcg/mL) mean (range)	11.9* (0.15-44.6)	44.4 (13.4-88.1)	46.6 (22.4-97.0)	38.5 (9.3-73.2)

*Orencia Label, steady state trough concentration, Section 12.3

(Source – Table 10.2-1, Study IM101301 2-5yrs report)

- Comparable steady state trough concentrations across age groups were achieved by Day 85 following the weekly body-weight–tiered subcutaneous dosing regimen in JIA patients 2-17 years old (Table 2).

Table 2. Observed steady state Cmin of abatacept in different age groups

	Pediatric (6 -17 yrs)	**Pediatric (2-5 yrs)**	**Pediatric (6-11 yrs)**	**Pediatric (12-17 yrs)**
Route	IV	SC	SC	SC
Day 85				
N	N/A	25	61	84
Cminss (mcg/mL) mean (range)	11.9* (0.15-44.6)	50.8 (31.1-83.4)	44.5 (18.8-82.5)	37.8 (7.4-97)
Day 113				
N	N/A	19	59	72
Cminss (mcg/mL) mean (range)	11.9* (0.15-44.6)	50.1 (26.4-88.1)	46.5 (13.4-88.1)	38.6 (9.3-97)

* Orencia Label, steady state trough concentration, Section 12.3

(Source – Table 10.1-1, Study IM101301 2-5yrs report ; Table 7.4.2.2-1, Study IM101301 6-17yrs report)

- Abatacept exposure (Cmin, Cmax and AUC) is predicted to be similar in adult RA patients and pediatric JIA patients following the proposed subcutaneous dosing regimen (see Section 2.4.3). Despite a higher Cmin (Table 1, Table 2), the overall abatacept exposure (AUC) is lower with the weekly subcutaneous dosing regimen as compared to IV dosing regimen (Figure 1).

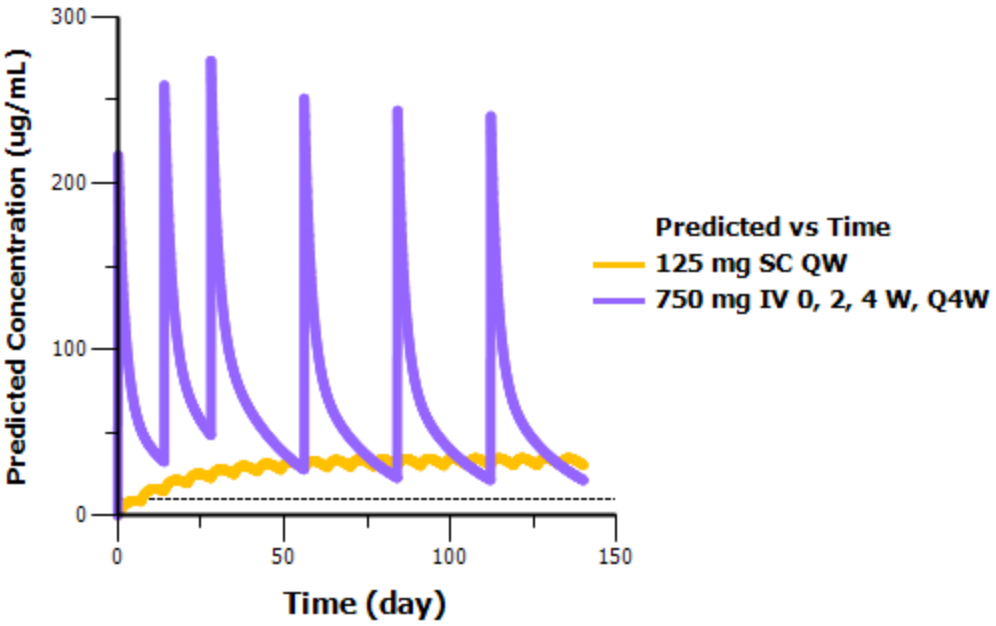


Figure 1. Simulated abatacept concentration vs time with SC and IV dosing regimens
(Source: Reviewer analysis)

- SC abatacept was associated with low overall immunogenicity rates (~3.5%, 7/202) based on the ECL immunoassay (See OBP review for assay assessment). Anti-abatacept antibodies had no clear impact on the PK, safety, or efficacy of abatacept.
- Based on clinical pharmacology review, the information provided in the final study report IM101301 is acceptable for the fulfillment of the written request from a clinical pharmacology perspective.

2. Question Based Review

Abatacept has been reviewed previously under BLA125118 (Initial approval 2005). For brevity purposes, only QBR questions relevant to this supplement will be addressed.

2.1 Regulatory history

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Abatacept is a fully human, recombinant, soluble fusion protein consisting of the extracellular

domain of human CTLA4 and a fragment of the Fc region of human IgG1. In December 2005 and April 2008, Orencia® (abatacept) was approved for IV use in the United States for the treatment of adults with RA and children with active JIA, respectively.

In July 2011, the SC formulation of abatacept was approved in the U.S. for the treatment of adults with RA. Currently, SC formulation is available both as PFS and autoinjector. The approved and proposed dosing regimens for RA and JIA are summarized in Table 3.

Table 3. Summary of abatacept dosing regimen

Route	RA	PJIA (≥6 yr)
IV (Initial approval for RA 2005; approved for JIA 2008, lyophilized powder)	< 60 kg, 500 mg; 60-100 kg,750 mg; >100 kg ,1000 mg Doses should be given at weeks 0, 2 and 4 and every 4 weeks thereafter	<75kg, 10 mg/kg; ≥75 kg, adult dose Doses should be given at weeks 0, 2 and 4 and every 4 weeksthereafter
Subcutaneous (PFS, approved 2011; Autoinjector 125 mg)	125 mg QW Optional IV loading dose	10 to< 25 kg, 50 mg QW; 25 to <50 kg, 87.5mg QW; ≥50 kg ,125 mg QW

*Approved dosing regimen in black; proposed dosing regimen in red
(Source: reviewer summary)

There have been several interactions between the Agency and the Sponsor to discuss the overall development program for abatacept SC in PJIA, as listed in Table 4.

OSI inspection was requested for study IM101301 (analytical lab, validation report and analytical study report), and the inspection result by Office of Study Integrity and Surveillance (OSIS) is still pending at the time of this review.

Table 4. Summary of Regulatory history relevant to clinical pharmacology

Type C meeting request/package by BMS (May 2011)	BMS proposed (b) (4)
FDA written response (Jun 2011)	1. "Given what is already known about the efficacy of IV and SC abatacept, a (b) (4) is not necessary." 2. "the pediatric SC study of abatacept in JIA patients could be a PK study with an open-label safety assessment of sufficient duration to assess adverse events with longer latency (i.e. 6-12 months)." 3. "Consistent with this information (*prior E-R knowledge with SC, IV abatacept in RA and IV abatacept in PJIA*), you proposed a body-weight tiered dosing plan to achieve a range of serum concentrations that is comparable to the adult range and specifically achieving trough concentrations above 10 mcg/mL and at the same time not exceeding the upper limit of the concentrations achieved in adults. The above approach of pediatric dose selection based on prior E-R knowledge in adults and

	children appears reasonable." 4. "The Agency had previously waived further studies in JIA patients ages 2-5 years due to the product possibly being unsafe in an immature developing immune system based on juvenile animal studies."
Written request issued (Sep 2013)	• Requested clinical studies: • Study 1: A pharmacokinetic and safety study of subcutaneous (SC) abatacept in PJIA patients 6 to 17 years of age. o Efficacy of SC abatacept will be supported by demonstrating the proposed SC abatacept regimen is able to achieve the steady state trough concentration (Cmin) associated with efficacy in the IV abatacept PJIA study used to support the approval of abatacept for PJIA. • Study 2: Interim results from the long-term safety registry of abatacept in PJIA patients 6 to 17 years of age.

(Source: reviewer summary)

2.1.2 Is the clinical pharmacology portion of written request fulfilled?

Yes, the written request is considered to be fulfilled from a clinical pharmacology perspective. See Table below.

Written request (clin pharm related)	**Fulfilled**
Study 1:Efficacy of SC abatacept will be supported by demonstrating the proposed SC abatacept regimen is able to achieve the steady state trough concentration (Cmin) associated with efficacy in the IV abatacept PJIA study used to support the approval of abatacept for PJIA.	**Yes (section 2.5.1)**
Study 1: The primary objective of the study is to estimate abatacept steady state trough concentration (Cmin) in children and adolescents with PJIA 6 to 17 years of age. *Secondary objectives will include assessment of efficacy and safety of abatacept administered subcutaneously in PJIA patients and assessment of Cmin as agreed upon with the agency by each weight-tiered dosing category. Weight-tiered dosing is intended to accommodate fixed subcutaneous doses while maintaining systemic exposure within the target therapeutic range defined by the previously performed IV PJIA study.*	**Yes (See Table 7)**
Pharmacokinetic Endpoints: *The pharmacokinetic endpoints for Study #1 must include abatacept steady-state trough concentration (Cmin) at Day 113 and abatacept Cmin at Day 57, Day 85, and Day 113 by weight tiered dosing categories (<25 kg, 25 to <50 kg, and >50 kg).*	**Yes (See Table 6)**
Number of patients to be studied: *Study 1: Enroll 160 patients with PJIA 6 to 17 years of*	**Yes, 173 subjects were enrolled and treated (Table**

age for safety and PK. This should include a sufficient number of patients 6 to 10 years old, and 12 to 17 years old to assess PK by weight-tiered dosing categories.	**12).**
Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.	**Yes. (Table 12, Appendix 4.1, individual study review)**
Drug information: *Study 1:* • *dosage form* o *Abatacept solution for SC injection* • *route of administration* o *SC* • *regimen* o *Patients will receive a weekly dose of SC abatacept based on their weight. Patients weighing <25 kg will receive 50 mg. Patients weighing 25 to <50 kg will receive 87.5 mg. Patients weighing >50 kg will receive 125 mg.*	**Yes (Appendix 4.1, individual study review)**

2.2 General Attributes of the Drug and pediatric formulation

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug Substance

Orencia® (abatacept) is a soluble fusion protein that consists of the extracellular domain of human CTLA-4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1. Abatacept is produced by recombinant DNA technology in a mammalian cell expression system. The apparent molecular weight of abatacept is 92 kilodaltons. The drug substance used for the SC formulation and the IV formulation is the same.

Drug Product

Abatacept Injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale-yellow solution with a pH range of 6.8 to 7.4 for subcutaneous administration. ORENCIA Injection is supplied as a single-dose prefilled syringe (50, 87.5, or 125 mg) or as a single-dose ClickJect autoinjector (125 mg, see Table 4). The drug product composition and concentration is the same across the approved presentation, clinical presentation, and additional commercial presentations.

Table 4. Contents of ORENCIA Subcutaneous Injection

Presentation	Active Ingredient Quantity and Label Volume	Inactive Ingredient Content
ORENCIA Injection	1 mL of a 125 mg/mL	dibasic sodium phosphate anhydrous (0.838 mg)

125 mg Prefilled Syringe and ClickJect Autoinjector	solution of abatacept (125 mg Dose)	monobasic sodium phosphate monohydrate (0.286 mg) poloxamer 188 (8 mg) sucrose (170 mg) qs to 1.0 mL water for injection
ORENCIA Injection 87.5 mg Prefilled Syringe	0.7 mL of a 125 mg/mL solution of abatacept (87.5 mg Dose)	dibasic sodium phosphate anhydrous (0.587 mg) monobasic sodium phosphate monohydrate (0.200 mg) poloxamer 188 (5.6 mg) sucrose (119 mg) qs to 0.7 mL water for injection
ORENCIA Injection 50 mg Prefilled Syringe	0.4 mL of a 125 mg/mL solution of abatacept (50 mg Dose)	dibasic sodium phosphate anhydrous (0.335 mg) monobasic sodium phosphate monohydrate (0.114 mg) poloxamer 188 (3.2 mg) sucrose (68 mg) qs to 0.4 mL water for injection

(Source: Table 4, proposed package insert of Orencia)

2.2.1 What is the proposed mechanism of action and therapeutic indication?

MOA: Abatacept is a selective costimulation modulator that blocks the interaction between the costimulatory molecules CD80/CD86 on antigen presenting cells and CD28 on T cells. This interaction provides a key signal necessary for full activation of T cells. By inhibiting CD28-mediated signaling, abatacept blocks antigen recognition and modulates the immune response to decrease T cell activation and its downstream effector functions.

Indication: The enclosed supplement provides data to support the use of SC abatacept for the following proposed indication that is identical to that of the approved indication for IV abatacept in JIA:

"*ORENCIA is indicated for reducing signs and symptoms in* (b) (4) *of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis. ORENCIA may be used as monotherapy or concomitantly with methotrexate (MTX).*"

2.2.2 What is the proposed dosing regimen and route of administration?

Table 5. Summary of abatacept dosing regimen

Route	RA	PJIA (≥6 yr)
IV (Initial approval for RA 2005; approved for JIA 2008, lyophilized powder)	< 60 kg, 500 mg; 60-100 kg,750 mg; >100 kg ,1000 mg Doses should be given at weeks 0, 2 and 4 and every 4 weeks thereafter	<75kg, 10 mg/kg; ≥75 kg, adult dose Doses should be given at weeks 0, 2 and 4 and every 4 weeksthereafter
Subcutaneous (PFS, approved 2011; Autoinjector 125 mg)	125 mg QW Optional IV loading dose	10 to< 25 kg, 50 mg QW; 25 to <50 kg, 87.5mg QW; ≥50 kg ,125 mg QW

*Approved dosing regimen in black; proposed dosing regimen in red
(Source: reviewer summary)

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

In order to support the efficacy of SC abatacept in JIA, it was considered reasonable to extrapolate the efficacy of SC abatacept from the IV abatacept JIA data based on PK bridging, given that abatacept IV is proven safe and effective in RA and JIA (ages ≥ 6 yrs). Based on the results of the E-R analysis in JIA following IV abatacept administration, and the results of the E-R analysis in RA following SC and IV administration, it was considered desirable to achieve an abatacept Cminss above 10 mcg/mL, which is associated with near maximal efficacy (FDA written response Jun 30, 2011).

As agreed by the Division and stated in the written request, the efficacy of SC abatacept in JIA patients was supported by demonstrating the proposed SC abatacept regimen is able to achieve the steady state trough concentration (Cmin) associated with efficacy in the IV abatacept JIA study used to support the approval of abatacept for JIA. This NDA contains the following clinical pharmacology studies:

- The Phase 3 Study IM101301 was an open-label study to assess PK, efficacy, safety, and immunogenicity of a weekly weight-tiered SC abatacept dosing regimen in subjects with JIA and prior intolerance or insufficient response to first-line and possibly second-line anti-rheumatic therapies.
- The data from the Phase 3 SC JIA Study IM101301 were combined with the data from clinical trials in patients with JIA (who received IV infusion, Phase 3 IV JIA Study IM101033) and in adult patients with RA (who received IV or SC abatacept) in order to perform PPK and E-R analyses.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

As stated in the written request, the efficacy of SC abatacept was extrapolated from the IV abatacept JIA data based on PK bridging. Based on E-R analysis (section 2.5.1), steady state trough concentration (Cminss) is the most relevant abatacept PK parameter for efficacy in RA and JIA. An abatacept Cminss above 10 mcg/mL is the pharmacodynamically -linked pharmacokinetic target associated with near maximal efficacy. Therefore, the primary endpoint for study IM101301 is abatacept steady-state trough concentration (Cminss) at Day 113. Efficacy endpoints such as JIAACR30, JIAACR50, JIAACR70, and JIAACR100 were also assessed. For safety and efficacy results, please refer to the clinical review by Dr. Keith Hull.

2.4 Abatacept Exposure in pediatric patients

2.4.1 Is the proposed SC abatacept regimen able to achieve the steady state trough concentration (Cmin) associated with efficacy in the IV abatacept JIA study in patients 6 years and above?

Yes, a weekly weight-tiered SC abatacept dosing regimen achieved the desired therapeutic target Cmin (≥ 10 mcg/mL) in 149 out of 150 evaluable PK subjects at Day 113. In Study IM101301

among patients 2 to 17 years of age, steady-state of abatacept was achieved by Day 85 following the weekly body-weight–tiered subcutaneous abatacept dosing. The mean (range) trough concentration of abatacept at Day 113 (short-term) was 44.4 mcg/mL (13.4 to 88.1 mcg/mL), 46.6 mcg/mL (22.4 to 97.0 mcg/mL), and 38.5 mcg/mL (9.3 to 73.2 mcg/mL) in JIA patients weighting 10-<25kg, 25-<50kg, and ≥ 50 kg respectively (Table 6), compared to the steady state Cmin at 11.9 mcg/mL (0.15 to 44.6 mcg/mL) in the IV abatacept study. Comparable trough concentrations across weight tiers and age groups were observed by the body-weight–tiered subcutaneous dosing regimen in JIA patients 2-17 years old (Figure 2).

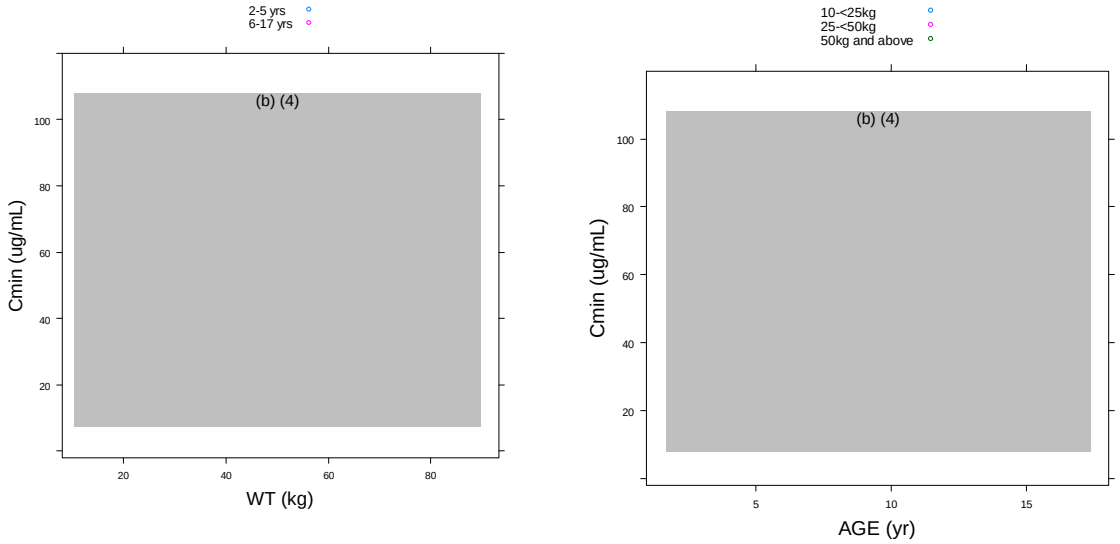


Figure 2. Observed Cmin of abatacept on Day 113 across age-groups and wt-groups with the weekly body-weight–tiered subcutaneous abatacept dosing (Study IM101301)
(Source: Reviewer analysis)

Table 6. Summary Statistics of Abatacept Cmin Values During Short-term Period by Weight-Tiered Dose - Evaluable PK Population - 2-17 Year-old Age Group

	CMIN (ug/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
50mg			
N	40	42	34
MEAN	40.4	42.4	44.4
S.D.	13.3	16.6	15.6
GEO. MEAN	38.2	38.9	41.5
%CV	33	39	35
MEDIAN	39.1	40.0	43.7
MIN	13.6	8.1	13.4
MAX	79.0	83.4	88.1
87.5mg			
N	70	63	61
MEAN	39.1	44.9	46.6
S.D.	13.8	14.5	15.8
GEO. MEAN	36.5	42.5	44.2
%CV	35	32	34
MEDIAN	37.2	44.0	45.1
MIN	10.4	13.3	22.4
MAX	72.0	80.8	97.0
125mg			
N	74	65	55
MEAN	35.0	39.3	38.5
S.D.	11.6	15.9	12.0
GEO. MEAN	33.0	36.0	36.6
%CV	33	40	31
MEDIAN	32.7	38.6	37.2
MIN	9.0	7.4	9.3
MAX	72.0	97.0	73.2

Weight Tiered Dose is based on first dose the patient received.

(Source – Table 10.2-1, Study IM101301 2-5yrs report)

Table 7. Summary Statistics of Abatacept Cmin Values During Short-term Period by Age - Evaluable PK Population - 2-17 Year-old Age Group

2-5 year

	CMIN (µg/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
N	27	25	19
MEAN	46.4	50.8	50.1
S.D.	13.0	14.3	14.2
GEO. MEAN	44.7	49.0	48.3
%CV	28	28	28
MEDIAN	46.6	47.6	50.2
MIN	25.9	31.1	26.4
MAX	79.0	83.4	88.1

6-11 year

	CMIN (µg/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
N	65	61	59
MEAN	38.4	44.5	46.5
S.D.	11.7	15.0	14.8
GEO. MEAN	36.4	42.0	44.0
%CV	31	34	32
MEDIAN	37.8	41.1	46.0
MIN	10.4	18.8	13.4
MAX	60.8	82.5	88.1

>=12 year

	CMIN (µg/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
N	92	84	72
MEAN	34.8	37.8	38.6
S.D.	12.8	15.2	13.6
GEO. MEAN	32.4	34.6	36.4
%CV	37	40	35
MEDIAN	32.4	36.8	36.4
MIN	9.0	7.4	9.3
MAX	72.0	97.0	97.0

(Source – Table 10.1-1, Study IM101301 2-5yrs report ; Table 7.4.2.2-1, Study IM101301 6-17yrs report)

2.4.2 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?

In patients 6 years and above, the effect of covariates on PK parameters can be visualized in Figure 3. The final PPK model, given the data, includes effects of baseline body weight, GFR, albumin, swollen joint count, co-administration of NSAID, and gender on CL, baseline body weight and age on VC, and baseline body weight on VP. Baseline body weight is the only variable that is considered clinically relevant, which is consistent with the results for the weight-based or weight-tiered dosing regimen. No dose adjustment was recommended for with respect to any of the other covariates. Overall, the result of covariate analysis suggested that disease (JIA versus RA) was not a significant covariate on clearance or volume of distribution of abatacept.

Reviewer's comments: *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 pop PK analysis. Nevertheless, the dataset included data from the lowest weight group (10-25kg), and age is not a significant covariate in the final PK model. Therefore, this reviewer does not expect that there would be other clinically significant covariates in addition to body weight.*

An information request (IR) was sent to the sponsor for sensitivity analysis, to include PK data in patients 2-5-yr-old in the pop PK analysis. The 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 this review, the IR is still pending.

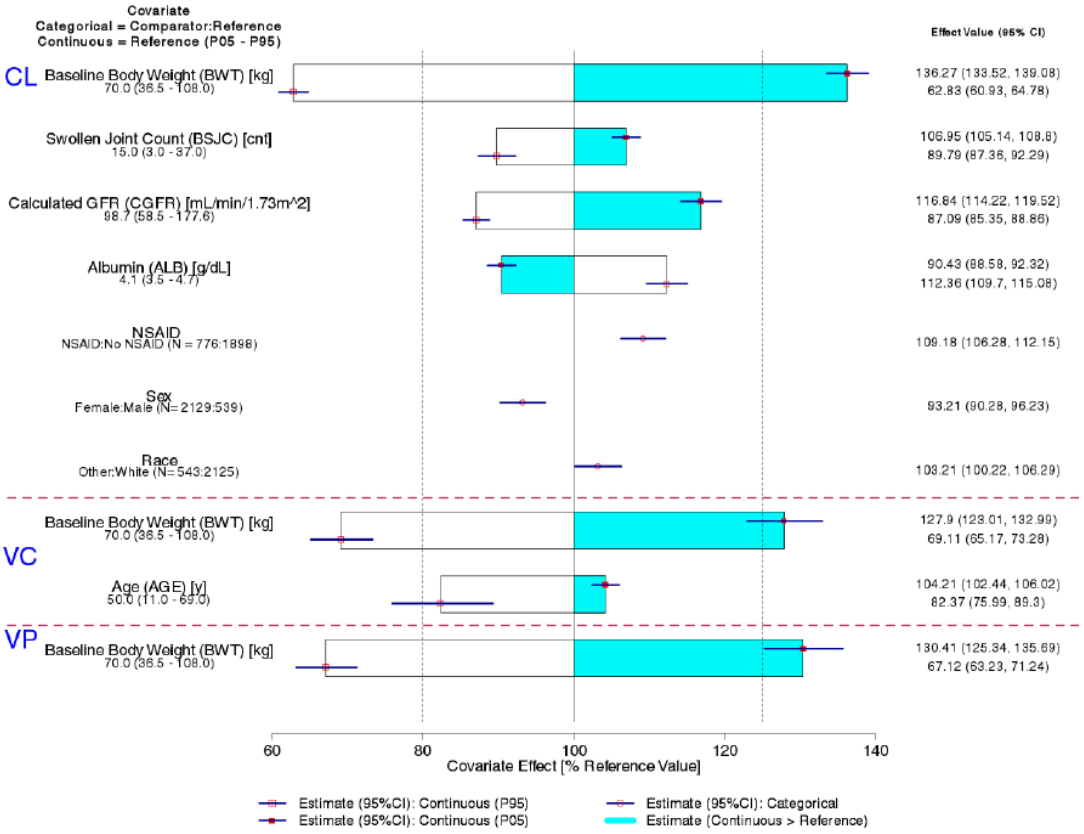


Figure 3. Impact of covariates on PK parameters displayed as ratio- or percentage with 90% CI comparing to a reference patient
(Source: Figure 5.1.1.2-1, Study report POH0428)

2.4.3 Is the exposure in pediatric JIA patients comparable to the exposure in adult RA patients following the proposed SC abatacept dosing regimen?

Overall, the exposure in PJIA patients is comparable to the exposure in adult RA patients. There is significant overlap in predicted steady state abatacept concentrations (Cmin, Cmax and Cave) in JIA and RA following the weekly SC abatacept administration, as shown in **Figure 4**. The estimated clearance is ~0.28 mL/h/kg in RA patients and ~0.36 mL/h/kg in JIA patients. .

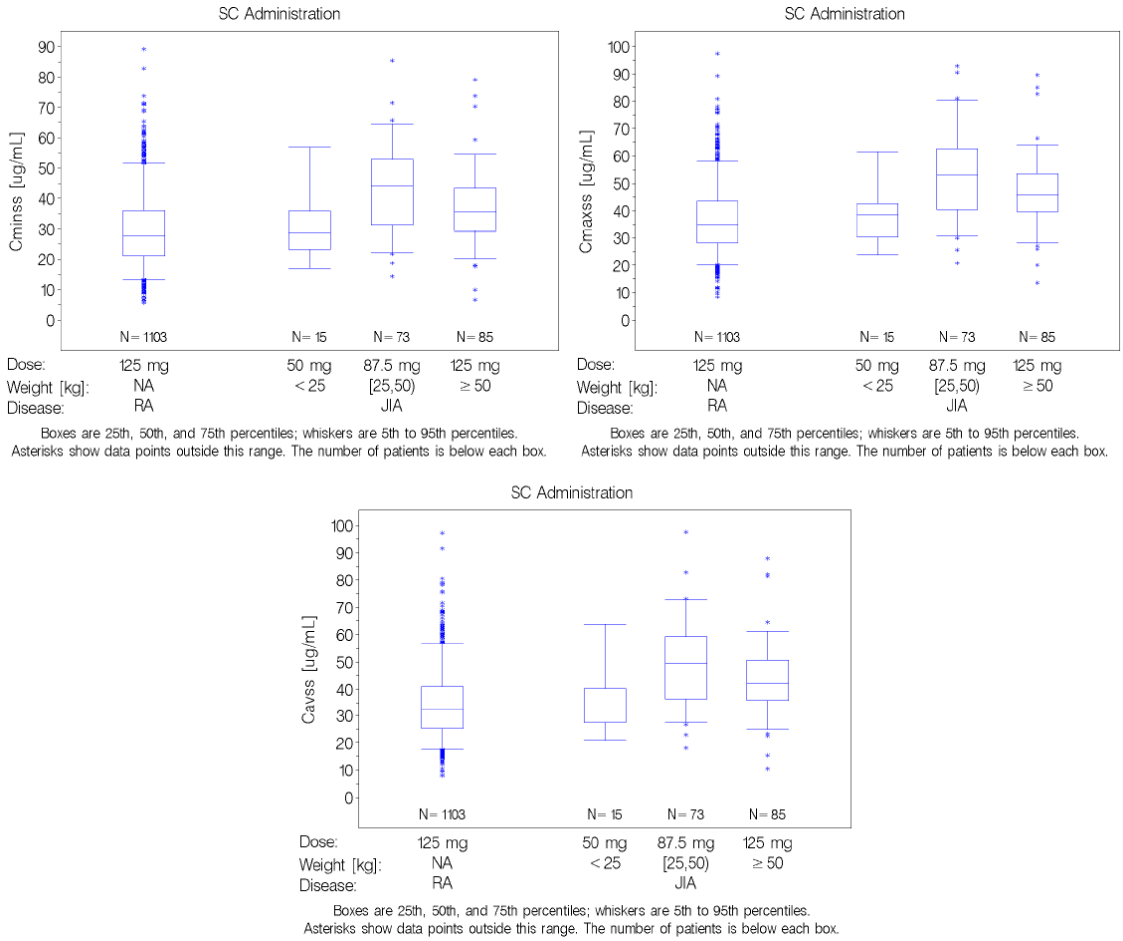


Figure 4. Predicted Distribution of Abatacept Steady-State Exposures Following SC Administration in JIA and RA Patients, by Dose
(Source: Figure 3.2.1-2, Summary of clinical pharmacology)

2.5 Exposure-Response

2.5.1 What are the characteristics of the exposure-response relationship for effectiveness?

E-R relationship in RA

Cminss is the most relevant abatacept PK parameter for efficacy in RA. In previous adult RA submissions, the E-R relationship in RA suggested that Cminss (trough serum concentration at steady-state) values of 10 µg/mL and higher were associated with near maximal efficacy in terms of the probability of achieving ACR20 and maximal reduction in disease activity score 28 joint count C-reactive protein (DAS28-CRP). In the clinical studies, the SC formulation had comparable efficacy compared to the IV formulation (Table 8), despite the different PK profiles with the SC and IV dosing regimens (Figure 5). Both IV and the SC delivered steady-state Cmin concentrations at or above 10 µg/mL, suggesting that Cminss is the most relevant abatacept PK parameter for efficacy.

Table 8. Proportion of RA Patients with ACR20 Response at Day 169 (Per Protocol Analysis): Per Protocol Population in Short-Term Period of Study IM101174

ACR20 Response Day 169	SC Aba + MTX N=693	IV Aba + MTX N=678
Responders (%) (95% CI)	527 (76.0%) (72.9, 79.2)	514 (75.8%) (72.6, 79.0)
Estimate of Difference (95% CI)	0.3 (-4.2, 4.8)	NA

Abbreviations: Aba: abatacept; CI: confidence interval; N: number of patients; NA: not applicable

(Source: Table 6.3.2 of IM101174 CSR)

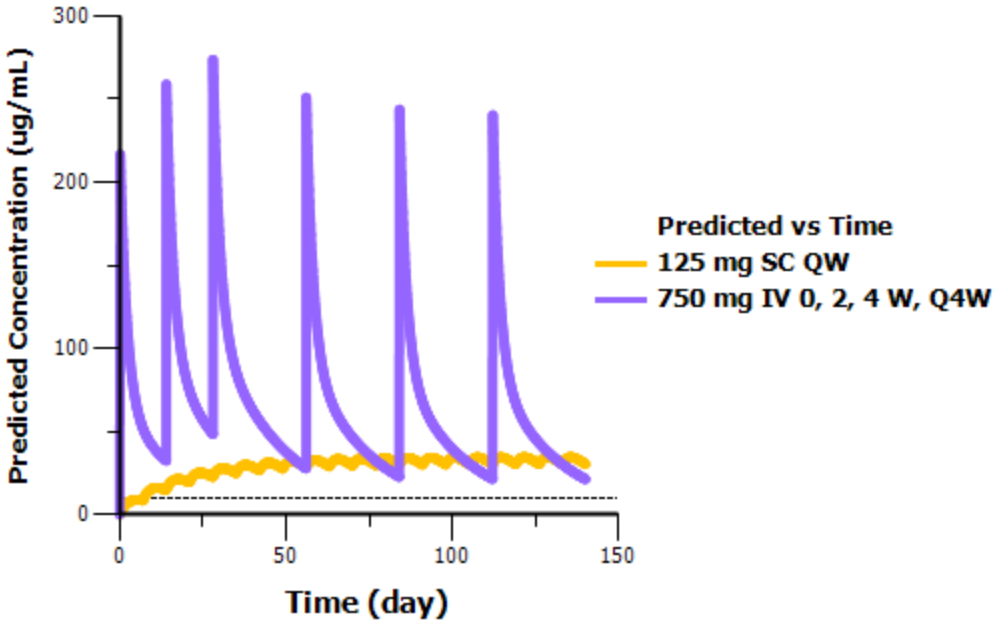
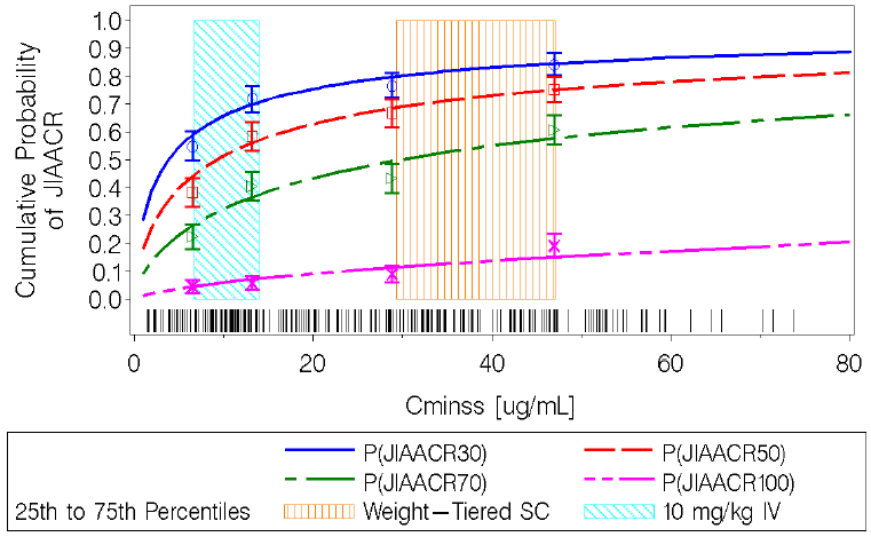


Figure 5. Simulated abatacept concentration vs time with SC and IV dosing regimens
(Source: Reviewer analysis)

E-R relationship in JIA

The E-R relationship for JIAACR was best described by a log linear function of Cminss. In the JIAACR model, it was identified that abatacept Cminss (compared to Cmaxss and Cavss) was the best measure of exposure for predicting the JIAACR. The probability of achieving a JIAACR response (JIAACR30, JIAACR50, JIAACR70, and JIAACR100) at 4 months was found to increase with increasing Cminss (Figure 6). No covariates were identified to significantly influence the E-R relationship for JIAACR responses.

For IV administration of abatacept, Cminss of 10 mcg/mL was associated with the near maximal JIAACR30 efficacy response in JIA patients. At the observed range of Cminss for weight-tiered weekly SC administration of abatacept, the probability of JIAACR response was reaching a plateau.



The lines represent the model—based predicted probability of JIAACR responder. The symbols represent the median Cminss of the grouped data and associated observed probabilities. The bars around the symbols represent the standard errors of the observed proportions. The hash marks near the x—axis represent the individual Cminss for JIAACR responders.

Figure 6. Observed and Predicted Probability of JIAACR Response at Month 4 (Study IM101301 and IM101033)
(Source: Figure 3.3.1.1-1, summary of clinical pharmacology)

Reviewer comment:

Written request	Fulfilled
Study 1:Efficacy of SC abatacept will be supported by demonstrating the proposed SC abatacept regimen is able to achieve the steady state trough concentration (Cmin) associated with efficacy in the IV abatacept PJIA study used to support the approval of abatacept for PJIA.	**Yes**

2.5.2 What are the characteristics of the exposure-response relationships for safety?

The PK profile of abatacept following the SC and IV dosing regimens are shown in Figure 5. Except for a higher Cmin, the exposure (AUC and C_{max}) with abatacept SC dosing regimen is much lower compared to those of the abatacept IV dosing regimen (Figure 5). No new safety signals were observed in Study IM101301. These results indicate that SC administration of abatacept causes no unique safety issues in the JIA population relative to the same population treated with IV abatacept or to adults with RA.

Exploratory E-R analysis was performed by graphical examination of the relationship between summary measures of abatacept exposures (Cminss, Cmaxss, and Cavss) and the occurrence of infection adverse events (AEs). Other AEs (eg, malignancies, autoimmune disorders, local

injection-site reactions, AEs within 24 hours of drug administration) were rare, and therefore were not included in the E-R analysis.

Based on graphical exploration (Figure 7), there was no relationship between abatacept systemic exposure (Cminss, Cavgss, and Cmaxss) and the incidence of infection within the exposure range tested in the JIA studies. This is consistent with that observed in the adult RA studies for both IV and SC abatacept.

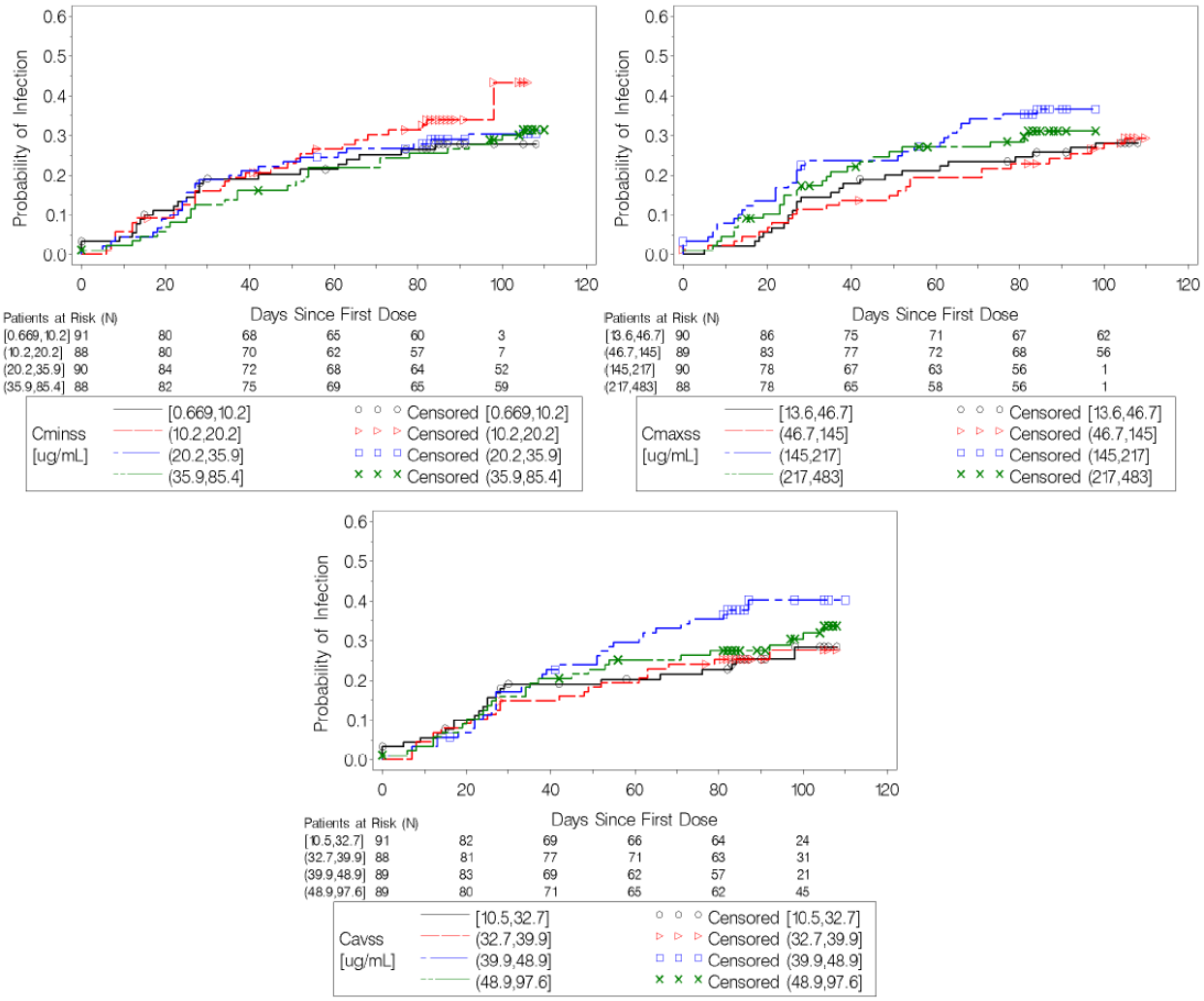


Figure 7. Kaplan-Meier Plots of Probability of First Infection Regardless of Seriousness Versus Days by Quartiles of Abatacept Exposure (IV and SC)

(Source: Figure 7, Summary Clin Pharm)

2.6 Analytical Section

2.6.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Serum concentrations of abatacept were analyzed using a validated enzyme-linked immunosorbent assay (ELISA). The PK assay was performed by (b) (4)). The assay measured abatacept in human serum using an anti-human CTLA4 capture antibody (clone 7F8) and a biotin labeled anti-human CTLA4 detection antibody

(clone 11D4). The calibration curve was generated using a 4 parameter logistic fit with 1/Y weighting. The validated range for this method in human serum is from 1.0 ng/mL to 30.0 ng/mL. See section 2.6.2 and 2.6.3 for detailed assay methodology and acceptance criteria.

2.6.2 What bioanalytical methods are used to assess concentrations of the measured moieties?

Analytical method for Abatacept: (b) (4) -0116 (validation study report # (b) (4) -355A); bioanalytical report # (b) (4) -054

An analytical method was developed and validated for the determination of abatacept in human serum and used to quantify abatacept in study 101301.

In this colorimetric enzyme linked immunosorbent assay (ELISA) method, microtiter plates are coated with anti-CTLA4, a monoclonal antibody (clone 7F8) to capture abatacept in human serum samples. The captured CTLA4Ig (abatacept) is detected using a biotinylated monoclonal mouse antihuman CTLA4 antibody (clone 11D4) followed by streptavidin-horseradish peroxidase and measured using a TMB (3,3',5,5'-Tetramethylbenzidine) substrate. The optical densities produced are read at wavelengths 450 nm and 620 nm using a microplate reader.

Table 9. Bioanalytical Methods Validation Summary for Abatacept Quantitation (PK)

Validated Method	(b) (4) -0116
Matrix	Human Serum
Analyte	abatacept
Capture	Anti-CTLA4 monoclonal antibody, clone 7F8
Detector	biotinylated monoclonal mouse anti-human CTLA4 antibody (clone 11D4)
Regression Model, Weighting:	Logistic Auto Estimate (4-parameter, 1/Y)
Standard Curve	
LLOQ	1.0 ng/mL
ULOQ	30 ng/mL
QC Precision (% CV)	
Intra Assay	≤14.9%
Inter Assay	≤10.97%
QC Accuracy (% Deviation)	Within ±17.98%
Stability	
RT	5 Days
4°C	5 Days
-20°C	6.5 Months
-70°C or -80°C	9.75 Years
Freeze-Thaw	10 cycles

Source: (b) (4) Validation (b) (4) -355A,[4] BMS Validation Report no.51398[5]

Abbreviations: (b) (4) Immunoanalytical Method, LLOQ - Lower limit of quantification, QC - quality control, RT - room temperature, ULOQ - Upper limit of quantification.

(Source: Table 1.3.1-1, summary of biopharm, section 2.7.1)

Table 10. In-Study Assay Performance Summary

Clinical Study	Assay Method	Number of Runs	Accuracy (% Bias)[a] for Assay QCs	Precision (% CV)[b] for Assay QCs
IM101301	ELISA, (b) (4) 0116	52	-0.3 to 5.0	4.1 to 5.9

[a] Accuracy acceptance criteria: ± 20% of nominal

[b] Precision acceptance criteria: < 20%

(Source: Table 6, abatacept bioanalytical study report for IM101301)

2.6.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curves were validated over the concentration range of 1 to 30 ng/mL for abatacept (Calibrators at 1, 2.5, 5.0, 10. 15, 20, 25, and 30ng/mL, QCs at 1, 3, 12.5, 24 and 30ng/mL). The range of standard curve is lower than the concentrations observed in study IM101301. Serum samples from study IM101301 were diluted for the assay. Calibration curves were generated using logistic auto estimate (four parameter logistic), with weighting factor 1/Y.

2.6.3.1 What are the lower and upper limits of quantitation?

LLOQ and ULOQ for abatacept was 1 ng/mL and 30 ng/mL, respectively, using sample volumes of 24 µL human serum. A 1,000,000-fold dilution factor was validated for 10,000,000 ng/mL concentration of abatacept. Linearity of dilution factors including 100, 200, 500, 1000, 2000, 5000, 10,000, and 100,000 was also validated.

2.6.3.2 What are the accuracy, precision, and selectivity at these limits?

Accuracy and precision: All intra and inter-assay precision and accuracy values were within the acceptance criteria (≤20%; ≤25% at the LLOQ). All cross validation precision and accuracy values were within the acceptance criteria (≤(b) (4) %).

Selectivity: Ten individual lots of human Rheumatoid Arthritis serum were assayed un-spiked and spiked at a level (2.8ng/mL) between the LLOQ and LQC. Of the 10 serum lots that were tested, 2 of the lots tested above the LLOQ when assayed un-spiked; a total of 8 lots (80%) were within ±(b) (4) % of the spiked concentration.

2.6.3.3 What is the sample stability under conditions used in the study?

The stability characteristics of abatacept in human serum are summarized in Table 11. Per SOP, a stability evaluation is considered acceptable if the measured concentrations of the analyte in 67% of all stability samples (with (b) (4) % at each level) meet the criteria for precision (±(b) (4) % CV) and accuracy (±(b) (4) % Bias).

Table 11. Stability of abatacept in Human Serum

Stability	
RT	5 Days
4°C	5 Days
-20°C	6.5 Months
-70°C or -80°C	9.75 Years
Freeze-Thaw	10 cycles

(Source: Table 1.3.1-1, summary of biopharm, section 2.7.1)

2.7 Immunogenicity

2.7.1. What is the incidence (rate) of the formation of the anti-drug antibodies (ADA)?

Immunogenicity is low in Study IM 101301. Of the 171 JIA patients 6-17 years old, 4 (2.3%) tested positive for antibodies to abatacept relative to baseline. Of these, 2 subjects had immunogenicity that persisted for ≤ 3 consecutive test days. Of the 31 JIA patients 2-5 years old,3 (9.7%) tested positive for antibodies to abatacept relative to baseline. No subject had positive immunogenicity on consecutive scheduled test days.

The detection of anti-abatacept antibodies in human serum was performed using a validated bridging electrochemiluminescence (ECL) immunoassay. The ECL assay differentiated between 2 antibody specificities: (1) the immunoglobulin (Ig) G and/or junction region and (2) CLTA4 and possibly Ig. A 3-step process was used for the anti-abatacept ECL assay: screening, immunodepletion, and endpoint titer determination. For detailed information regarding the immunogenicity assay, refer to the OBP review.

2.7.2. What are the impacts of ADA on abatacept PK, efficacy and safety?

Anti-abatacept antibodies had no clear impact on the PK, safety, or efficacy of abatacept. Cminss levels of subjects with ADAs were comparable to the geometric mean Cminss of the study population and were consistent regardless of when ADAs were detected. No serious AEs occurred in subjects with ADAs, and none of the AEs were hypersensitivity reactions. Neither the occurrence nor timing of immunogenicity to abatacept appeared to correlate with efficacy, as the most subjects with positive ADAs in the ST period were also JIA ACR30 responders at the same timepoints.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below.

At the time of this review, there is a pending IR regarding the highlighted paragraph in the label, to confirm that the label statement is valid for JIA patients 2-17 years old (Also see section 4.2). The following comments were sent to the sponsor regarding the highlighted paragraph:

"*This paragraph is pending on the clinical pharmacology IR. Responses to the IR before Mar 24th will be reviewed for this submission cycle, and can be used to support the label statement. If you could not provide the response by Mar 24th, this paragraph will be deleted. If you still want to include this particular paragraph in the label after Mar 24th, you may choose to submit a labeling supplement later on.* |"

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Juvenile Idiopathic Arthritis - Subcutaneous Administration

(b) (4)

4. Appendix

4.1 Appendix 1. INDIVIDUAL STUDY REVIEW

1. Phase 3 study with Abatacept SC in PJIA

Study IM101301

Title: A Phase 3 Multi-center, Open-label Study to Evaluate Pharmacokinetics, Efficacy and Safety of Abatacept Administered Subcutaneously (SC) in Children and Adolescents with Active Polyarticular Juvenile Idiopathic Arthritis (pJIA) and Inadequate Response (IR) to Biologic or Non-biologic Disease Modifying Anti-rheumatic Drugs (DMARDs)

Objective:

Primary: To estimate abatacept steady-state trough concentration (Cminss) at Day 113 in children and adolescents with pJIA aged 6 through 17 years treated with subcutaneous (SC) abatacept.

Secondary:

- To assess ACR Pediatric 30 on Day 113.
- To assess safety.
- To assess abatacept Cmin at Day 57, Day 85, and Day 113 during the initial 4-month ST period by each weight-tiered dose in 6 through 17 year-old subjects.
- To assess the proportion of subjects with positive immunogenicity response during the initial 4 month period (6 through 17 year-old cohort only) and during the cumulative abatacept period up to 6 months following discontinuation of treatment (in both age cohorts)

Only results related to PK are reviewed here. For safety and efficacy results, please refer to the clinical review by Dr. Keith Hull. For cross study PK comparison with IV dosing regimen, please refer to pharmacometics review (Appendix 4.2)

Study design and treatment schedule:

This was an open-label study to assess PK, safety, and efficacy of SC abatacept in pJIA aged 2 to 17 years old with screening weights of ≥10 kg. The study design is shown in Figure 8.

Study Population: The study included 2 cohorts of subjects with active pJIA: a 2 through 5 year-old cohort (32 treated subjects as of August 2015) and a 6 through 17 year-old cohort (173 treated subjects). The younger cohort was evaluated in order to expand the clinical experience (primarily safety) of abatacept into this age group, and to fulfill a requirement from the EMA. The baseline demographics for the 6-17 year old cohort were listed in Table 12. The study population of 6-17 year old has met the WR requirement.

Table 12. Baseline Demographic Characteristics - All Treated Subjects - 6-17 Year-old Age Cohort

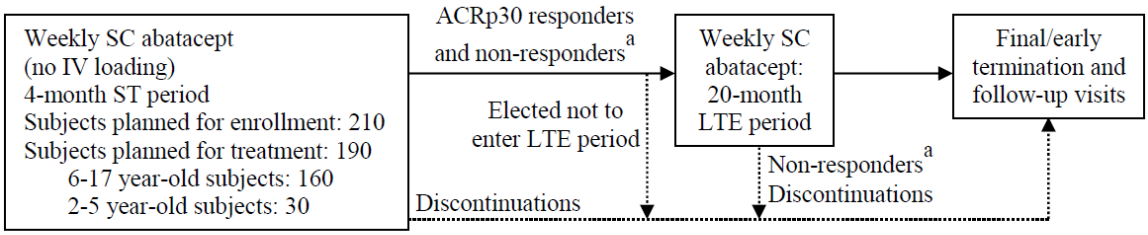
		Total N = 173
Age (years)	N	173
	Mean	12.3
	SD	3.1
	Median	13.0
	Min	6.0
	Max	17.0
Weight (Kg)	N	173
	Mean	46.5
	SD	18.8
	Median	45.0
	Min	16.0
	Max	146.3
Weight Categories	<25kg	18 (10.4%)
	25-50kg	74 (42.8%)
	>=50kg	81 (46.8%)
Gender	Male	37 (21.4%)
	Female	136 (78.6%)
Race	White	144 (83.2%)
	Black/African American	14 (8.1%)
	American Indian/Alaska Native	0
	Asian	0
	Native Hawaiian/Other Pacific Islander	0
	Other	15 (8.7%)
Ethnicity (US Only)	Hispanic/Latino	2 (9.1%)
	Not Hispanic/Latino	20 (90.9%)
Geographic Region	North America	22 (12.7%)
	South America	56 (32.4%)
	Europe	78 (45.1%)
	ROW	17 (9.8%)

Abbreviations: ROW = Rest of World
Baseline is Day 1 of the study or last measurement prior to short-term dose.
Weight Category is based on weight at baseline rounded to 1 integer to be consistent with IVRS assignment of weight tiered dose.

Reviewer comment:

Written request	**Fulfilled**
Number of patients to be studied: Study 1: Enroll 160 patients with PJIA 6 to 17 years of age for safety and PK. This should include a sufficient number of patients 6 to 10 years old, and 12 to 17 years old to assess PK by weight-tiered dosing categories.	**Yes**
Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.	**Yes**

Treatments: SC abatacept was administered weekly with 3 different PFS presentations for 3 weight tiers: 10 to < 25 kg (50 mg in 0.4 mL PFS), 25 to < 50 kg (87.5 mg in 0.7 mL PFS), and ≥50 kg (125 mg in 1 mL PFS). Abatacept was self-administered by the subject and/or legal representative after training or was administered during scheduled office visits by investigational staff. Subjects from both cohorts who completed the 4-month ST period were given the option to enter a 20-month LTE period where they continued to receive weekly SC abatacept injections.



[a]Non-responders per ACRp30 criteria by month 4 were given the opportunity to be treated with SC abatacept for an additional 3 months in the LTE period. If, after 7 total months of treatment, response did not occur, the subject was considered for discontinuation.

Figure 8. Study Design
(Source: Figure 4.1-1, study report IM101301)

Reviewer comment:

Written request	Fulfilled
Drug information: *Study 1:* • *dosage form* o *Abatacept solution for SC injection* • *route of administration* o *SC* • *regimen* o *Patients will receive a weekly dose of SC abatacept based on their weight. Patients weighing <25 kg will receive 50 mg. Patients weighing 25 to <50 kg will receive 87.5 mg. Patients weighing >50 kg will receive 125 mg.*	**Yes**

PK Sampling Schedule
There were two PK sampling schedules in this study.

- All subjects had pre-dose blood samples collected at Days 1, 57, 85 and 113.
- Approximately 60 of the subjects were enrolled into the PK sub-study. In addition to the pre-dose samples, PK samples were collected at day 2-4, 8, 29 and 43 (Table 13).

Table 13. Pharmacokinetic Sampling Schedule

Study Day	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample for All Subjects	PK Blood Sample for Sub-study Subjects
Short Term Period				
1	0 (predose)	00:00	X	
2-4	24h - 72h	48:00		X
8	0 (predose)	00:00		X
29	0 (predose)	00:00		X
43	0 (predose)	00:00		X
57	0 (predose)	00:00	X	
85	0 (predose)	00:00	X	
113	0 (predose)	00:00	X	

APPEARS THIS WAY ON ORIGINAL

Study Day	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample for All Subjects	PK Blood Sample for Sub-study Subjects
Long Term Extension Period				
Every 6 Months	0 (predose)	00:00	X	
Final/Early Termination & Follow up visits[a]				
Final/Early Termination Visit (~ 7 ± 3 days after last SC injection)[b]	168_	168:00_	X	
28 days after last SC injection (only required for subjects that early terminate from the study or complete the study and will not be continuing on abatacept)	672	672:00	X	
85 days after last SC injection (only required for subjects that early terminate from the study or complete the study and will not be continuing on abatacept)	2040	2040:00	X	
168 days after last SC injection (only required for subjects that early terminate from the study or complete the study and will not be continuing on abatacept)	4032	4032:00	X	

[a] Except for the final/early termination visit, samples will only be evaluated to determine serum drug concentration in the event that there is a corresponding CTLA4 positive immunogenicity result

[b] The samples for early termination/final visit are taken at the same time as other blood sample collection at early termination.

(Source: Table 5.5.1-1, study report IM101301)

Immunogenicity Sampling Schedule

Sample draws for immunogenicity were scheduled at specific study days while on treatment for all subjects and at follow-up visits 28, 85, and 168 days after the last abatacept dose for those subjects who discontinued from the ST period or completed the ST study without continuing abatacept treatment.

Results

Pharmacokinetics Results

Primary Endpoint: Abatacept Cmin at Day 113

A weekly weight-tiered SC abatacept dosing regimen achieved the desired target therapeutic Cmin (≥10 µg/mL) in 149 out of 150 evaluable PK subjects at Day 113. Comparable trough concentrations across weight tiers were delivered by the body-weight–tiered subcutaneous dosing regimen in PJIA patients 2-17 years old (**Table 14**). The geometric mean trough concentration of abatacept at Day 113 was 41.5 mcg/mL (13.4 to 88.1 mcg/mL), 44.2 mcg/mL (22.4 to 97.0 mcg/mL), and 36.6 mcg/mL (9.3 to 73.2 mcg/mL) in PJIA patients weighting 10-<25kg, 25-<50kg, and ≥ 50 kg respectively. Similar Cmin levels were observed at Day 57 and Day 85.

Table 14. Summary Statistics of Abatacept Cmin Values During Short-term Period by Weight-Tiered Dose - Evaluable PK Population - 2-17 Year-old Age Group

	CMIN (ug/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
50mg			
N	40	42	34
MEAN	40.4	42.4	44.4
S.D.	13.3	16.6	15.6
GEO. MEAN	38.2	38.9	41.5
%CV	33	39	35
MEDIAN	39.1	40.0	43.7
MIN	13.6	8.1	13.4
MAX	79.0	83.4	88.1
87.5mg			
N	70	63	61
MEAN	39.1	44.9	46.6
S.D.	13.8	14.5	15.8
GEO. MEAN	36.5	42.5	44.2
%CV	35	32	34
MEDIAN	37.2	44.0	45.1
MIN	10.4	13.3	22.4
MAX	72.0	80.8	97.0
125mg			
N	74	65	55
MEAN	35.0	39.3	38.5
S.D.	11.6	15.9	12.0
GEO. MEAN	33.0	36.0	36.6
%CV	33	40	31
MEDIAN	32.7	38.6	37.2
MIN	9.0	7.4	9.3
MAX	72.0	97.0	73.2

Weight Tiered Dose is based on first dose the patient received.

(Source – Table 10.2-1, Study IM101301 2-5yrs report)

Reviewer comment:

Written request	Fulfilled
Study 1: The primary objective of the study is to estimate abatacept steady state trough concentration (Cmin) in children and adolescents with PJIA 6 to 17 years of age. Secondary objectives will include assessment of efficacy and safety of abatacept administered subcutaneously in PJIA patients and assessment of Cmin as agreed upon with the agency by each weight-tiered dosing category. Weight-	**Yes**

tiered dosing is intended to accommodate fixed subcutaneous doses while maintaining systemic exposure within the target therapeutic range defined by the previously performed IV PJIA study.	
Pharmacokinetic Endpoints: *The pharmacokinetic endpoints for Study #1 must include abatacept steady-state trough concentration (Cmin) at Day 113 and abatacept Cmin at Day 57, Day 85, and Day 113 by weight tiered dosing categories (<25 kg, 25 to <50 kg, and >50 kg).*	**Yes**

Abatacept Cmin by age group

A steady state trough concentration of abatacept (Cminss) was further assessed by age subgroups in the 2 through 17 year-old evaluable PK population. The mean and ranges of Cminss at Day 113 between three age subgroups (2 -5 years, 6 -11 years, and ≥12 years) were comparable (**Table 15**).

Table 15. Summary Statistics of Abatacept Cmin Values During Short-term Period by Age - Evaluable PK Population - 2-17 Year-old Age Group

2-5 year

	CMIN (µg/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
N	27	25	19
MEAN	46.4	50.8	50.1
S.D.	13.0	14.3	14.2
GEO. MEAN	44.7	49.0	48.3
%CV	28	28	28
MEDIAN	46.6	47.6	50.2
MIN	25.9	31.1	26.4
MAX	79.0	83.4	88.1

6-11 year

	CMIN (µg/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
N	65	61	59
MEAN	38.4	44.5	46.5
S.D.	11.7	15.0	14.8
GEO. MEAN	36.4	42.0	44.0
%CV	31	34	32
MEDIAN	37.8	41.1	46.0
MIN	10.4	18.8	13.4
MAX	60.8	82.5	88.1

>=12 year

	CMIN (µg/mL)		
STATISTIC	DAY 57	DAY 85	DAY 113
N	92	84	72
MEAN	34.8	37.8	38.6
S.D.	12.8	15.2	13.6
GEO. MEAN	32.4	34.6	36.4
%CV	37	40	35
MEDIAN	32.4	36.8	36.4
MIN	9.0	7.4	9.3
MAX	72.0	97.0	97.0

(Source – Table 10.1-1, Study IM101301 2-5yrs report ; Table 7.4.2.2-1, Study IM101301 6-17yrs report)

Immunogenicity

Immunogenicity is low in Study IM 101301. Of the 171 JIA patients 6-17 years old, 4 (2.3%) tested positive for antibodies to abatacept relative to baseline. Of these, 2 subjects had immunogenicity that persisted for ⩽ 3 consecutive test days. Of the 31 JIA patients 2-5 years old, 3 (9.7%) tested positive for antibodies to abatacept relative to baseline. No subject had positive immunogenicity on consecutive scheduled test days.

Anti-abatacept antibodies had no clear impact on the PK, safety, or efficacy of abatacept. Cminss levels of subjects with ADAs were comparable to the geometric mean Cminss of the study population and were consistent regardless of when ADAs were detected. No serious AEs occurred in subjects with ADAs, and none of the AEs were hypersensitivity reactions. Neither the occurrence nor timing of immunogenicity to abatacept appeared to correlate with efficacy, as the most subjects with positive ADAs in the ST period were also JIA ACR30 responders at the same timepoints.

Results and Conclusions

In 2 through 17 year-old subjects with pJIA, a weekly body-weight-tiered SC abatacept dosing regimen:

- delivered therapeutic target abatacept Cmin levels of 10 mcg/mL or greater in > 99% of the evaluable PK population at Day 113.
- resulted in comparable Cminss exposure across weight-tiered doses at Day 113.
- was associated with low overall immunogenicity rates and associated antibody titers.

4.2 Appendix 2. PHARMACOMETRIC REVIEW

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 pop PK-ER report. This PM review was based on the sponsor's pop PK-ER report for patients 6 years above (2213 adult RA patients, 357 JIA patients age 6-17). Nevertheless, the datasets included data from the lowest weight group (10-25kg) in pediatric patients, and age is not a significant covariate in the final pop PK model. Also, the observed Ctrough data suggested that the abatacept exposure is comparable among age groups (Figure 9), and there were only 31 patients with evaluable PK data in the 2-5 yr old cohort. Therefore, this reviewer did not expect significant changes in the conclusions of a pop PK anlaysis with a dataset including 2-5- yr- old PK data. Also, as the exposure-response analysis for efficacy is to support efficacy extrapolation from the IV PJIA study IM101033, and the IV PJIA study only enrolled patients 6 years and above, the ER analysis in sponsor's pop PK-ER report is adequate.

An information request (IR) was sent to the sponsor for sensitivity analysis, to include PK data in patients 2-5-yr-old in the pop PK analysis. The 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 this review, the IR is still pending.

1. SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the proposed SC abatacept regimen is able to achieve the steady state trough concentration (Cmin) associated with efficacy in the IV abatacept PJIA study in patients 6 years and above?

Yes, a weekly weight-tiered SC abatacept dosing regimen achieved the desired target therapeutic Cmin (≥10 mcg/mL) in 149 out of 150 evaluable PK subjects at Day 113. In Study IM101301 among patients 2 to 17 years of age, steady-state of abatacept was achieved by Day 85 following the weekly body-weight–tiered subcutaneous abatacept dosing. The mean (range) trough concentration of abatacept at Day 113 (short-term) was 44.4 mcg/mL (13.4 to 88.1 mcg/mL), 46.6 mcg/mL (22.4 to 97.0 mcg/mL), and 38.5 mcg/mL (9.3 to 73.2 mcg/mL) in JIA patients weighting 10-<25kg, 25-<50kg, and ≥ 50 kg respectively (**Table 6**), compared to the steady state Cmin at 11.9 mcg/mL (0.15 to 44.6 mcg/mL) in the IV abatacept study. Comparable trough concentrations across weight tiers and age groups were delivered by the body-weight–tiered

subcutaneous dosing regimen in JIA patients 2-17 years old (Figure 9).

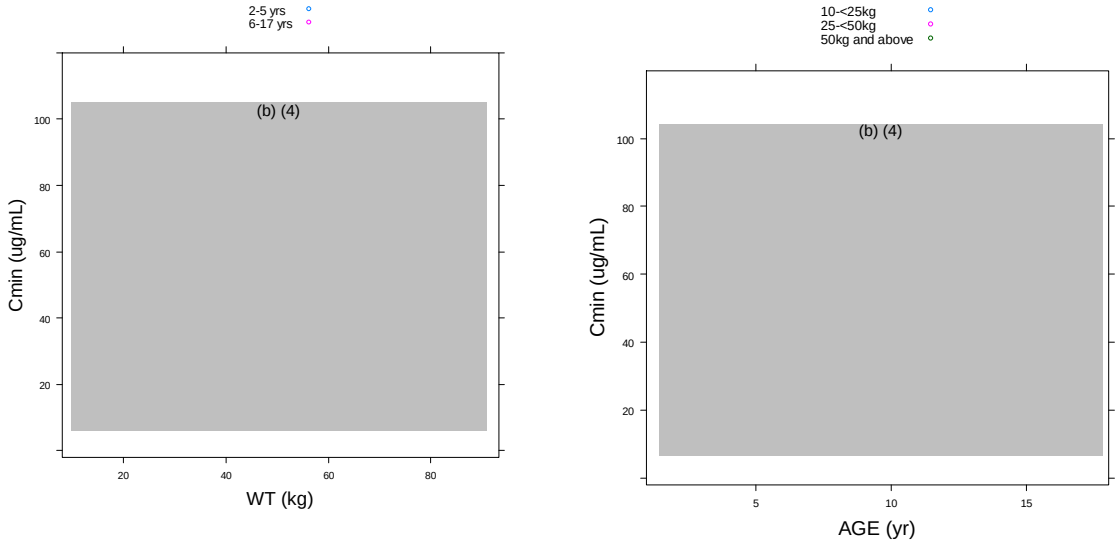


Figure 9. Observed Cmin of abatacept on Day 113 across age-groups and wt-groups with the weekly body-weight–tiered subcutaneous abatacept dosing (Study IM101301)
(Source: Reviewer analysis)

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

In patients 6 years and above, the effect of covariates on PK parameters can be visualized in Figure 10. The final PPK model, given the data, includes effects of baseline body weight, CGFR, ALB, swollen joint count, co-administration of NSAID, and gender on CL, baseline body weight and age on VC, and baseline body weight on VP. Baseline body weight is the only variable that is considered clinically relevant, which is consistent with the results for the weight-based or weight-tiered dosing regimen. No dose adjustment was recommended for with respect to any of the other covariates. Overall, the result of covariate analysis suggested that disease (JIA versus RA) was not a significant covariate on clearance or volume of distribution of abatacept.

The magnitude of all categorical covariate effects generally were encompassed within 80%-125% of reference values (**Figure 10**). The effect of baseline body weight on CL, VC, and VP exceeded the 80%-125% range, and was associated with a 36%, 28%, and 30% increase in CL, VC, and VP at the 95th percentile of BWT (108 kg), respectively; thus, this covariate effect is considered clinically relevant. The small effect of baseline age on VC (4%) was within the 80%-125% CI range, however the lower bound of the 95% CI associated with the 5th percentile of age (11 y) fell outside the 80% limit of the range. All other covariate relationships are completely contained within the 80%-125% range and therefore are not considered to be clinically relevant.

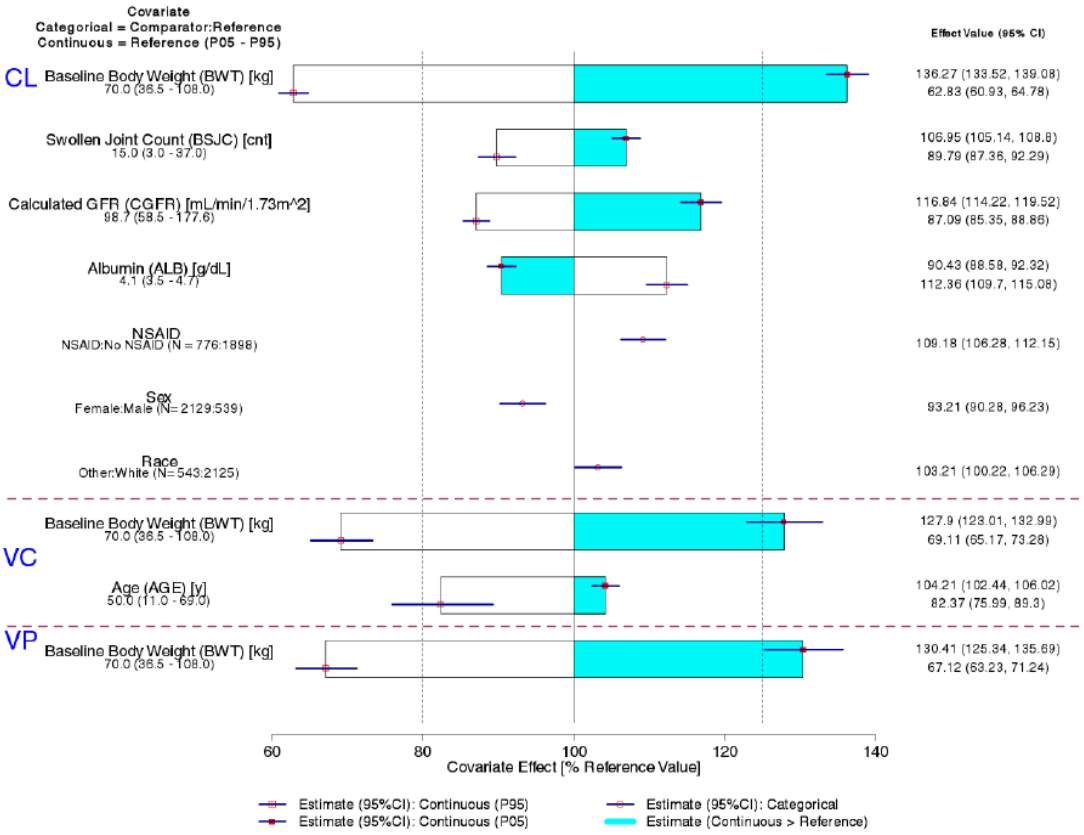


Figure 10. Impact of covariates on PK parameters displayed as ratio- or percentage with 90% CI comparing to a reference patient
(Source: Figure 5.1.1.2-1, popPK-ER report)

1.1.3 Is the exposure in pediatric JIA patients comparable to the exposure in adult RA patients following the proposed SC abatacept dosing regimen?

Overall, the exposure in PJIA patients is comparable to the exposure in adult RA patients. There is significant overlap in predicted steady state abatacept concentrations (Cmin, Cmax and Cave) in JIA and RA following the weekly SC abatacept administration, as shown in **Figure 11**. The estimated clearance is ~0.28 mL/h/kg in RA patients and ~0.36 mL/h/kg in JIA patients.

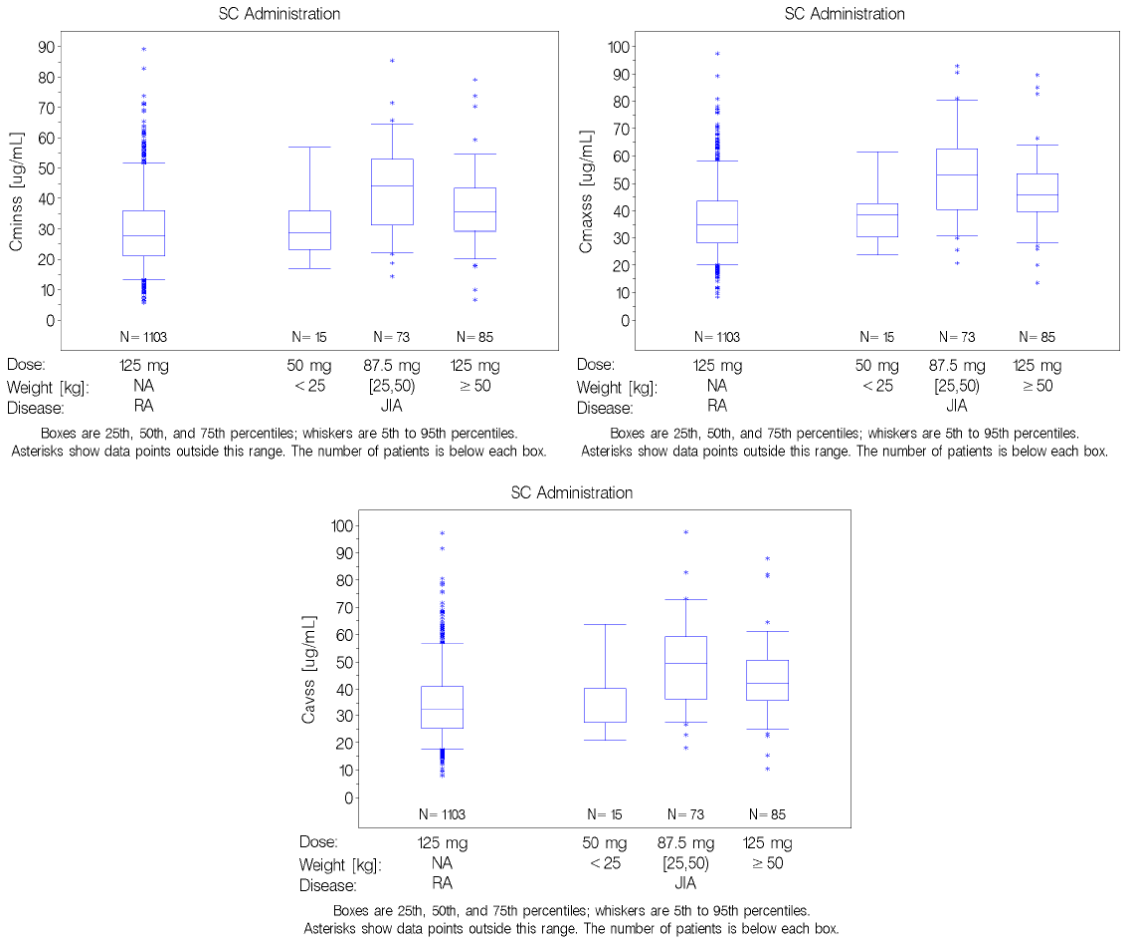


Figure 11. Predicted Distribution of Abatacept Steady-State Exposures Following SC Administration in JIA and RA Patients, by Dose
(Source: Figure 3.2.1-2, Summary of clinical pharmacology)

1.2 Recommendations

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in BLA 125118 (S211). This supplement is considered acceptable from a Pharmacometrics perspective.

1.3 Label Statements

Please refer to Section 3 - Detailed Labeling Recommendations in clinical pharmacology review.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK analysis

Primary objective of sponsor's population PK analysis was:

- To characterize the PK of abatacept following IV or SC administration in patients with JIA and to determine the effects of key covariates on abatacept PK parameters and exposure
- To provide individual abatacept exposure estimates to characterize the E-R relationships with respect to efficacy and safety endpoints of abatacept in JIA.

2.1.1 Data

The PPK analysis for abatacept was conducted with 12097 serum concentration values from 2213 patients with adult RA and 357 patients with JIA, ages 6 to 17, who received IV infusion (N = 184) or SC injection of abatacept (N = 173). Population PK analysis included the following 11 adult RA studies: 3 Phase 2 IV studies (IM103002, IM101100, and IM101101), 1 Phase 2 SC study (IM101063), 3 Phase 3 IV studies (IM101102, IM101029, and IM101031), and 4 Phase 3 SC studies (IM101167, IM101173, IM101174 [IM101174 PK substudy is also included], and IM101185) and the following 2 JIA studies: 1 Phase 3 IV study (IM101033) and 1 Phase 3 SC study (IM101301 [short-term and open-label periods]).

2.1.2 Method

The PPK model was developed in 3 steps. First, a base model was developed by estimating the parameters of the previously determined base model for JIA/ RA based on IV only with inclusion of an absorption component and pooled IV and SC JIAdata, assessing the influence of body weight (BWT) in the base model, and re-estimating parameters with inclusion of the pooled IV and SC adult RA data. Second, a full model was developed to assess the effect of disease, (JIA vs RA) and other selected covariates (Table 16) on abatacept CL and VC. Lastly, a parsimonious final model was developed by performing backward elimination on covariates added to the model during forward selection using 0.1% level of significance.

Table 16. Covariate-PK Parameter Relationships for Evaluation

Covariate Name	Description	Clearance	VC
Age	Continuous	X	X
Gender	Categorical (male versus female)	X	X
Race	Categorical (white versus non-white)	X	
Baseline Weight[a]	Continuous	X	X
Baseline Albumin	Continuous	X	
Baseline CGFR	Continuous	X	
Baseline Scr	Continuous	X	
Baseline Total Bilirubin	Continuous	X	
Duration of Disease at Baseline	Categorical (≤ 2 years, > 2 to 5 years, > 5 years to 10 years, > 10 years)	X	
Baseline Tender Joint Count[b]	Continuous	X	
Baseline Swollen Joint Count[b]	Continuous	X	
Baseline MTX Use	Categorical (yes versus no)	X	
Baseline anti-TNF Use	Categorical (yes versus no)	X	
Baseline Corticosteroid Use	Categorical (yes versus no)	X	
Baseline NSAID Use	Categorical	X	
Disease (JIA vs RA)	Categorical	X	

[a] Baseline weight was included as a statistically significant covariate on VC, VP and CL in base model

[b] In JIA, swollen joint count and tender (pain on motion and/or tenderness) joint count are subset of the count for active joints which is a component for JIAACR response definition.

(Source: Table 4.1.1.2-1, popPK-ER report)

2.1.3 Results

The PK of abatacept was characterized by a linear 2-compartment PPK model with zero-order IV infusion, first-order SC absorption, and first-order elimination with a combined residual error model (additive and proportional error). Disease (JIA vs RA) was not a statistically significant covariate in the PPK model. The model was parameterized in terms of bioavailability (F), firstorder KA, CL, VC, inter-compartmental clearance (Q), and volume of distribution of the peripheral compartment (VP).

Interindividual variability was estimated with random effects on CL, VC, VP, KA, and F. Analysis of covariate effects revealed that CL increased with BWT, calculated glomerular filtration rate (CGFR), and baseline swollen joint count (BSJC), decreased with albumin (ALB), and was lower in females while higher in patients on concomitant non-steroidal anti-inflammatory drugs (NSAIDs). Furthermore, VC and VP increased with BWT while VC also increased with age. Disease (JIA vs RA) was not a statistically significant covariate. Concentration values were similar for both anti-drug antibody (ADA) negative and positive status. The parameter estimates of the final model are shown in Table 17. Parameters were generally estimated with high precision. Baseline

body weight is the only variable that is considered clinically relevant, which is consistent with the results for the weight-based or weight-tiered dosing regimen. See section 1.1.2 for further analysis of the impact of covariates.

Table 17. Final parameter estimates for the final model

	Final Parameter Estimate		Interindividual Variability / Residual Variability[a]	
Parameter	**Estimate**	**%RSE**	**Estimate**	**%RSE**
KA: Absorption Rate Constant [1/h]	0.00789	20.7	0.661	42.4
VC: Central Volume [L][b]	3.36	1.52		
VC: Power of BWT on VC [-][c]	0.591	7.29	0.0505	13.7
VC: Power of Age on VC [-][c]	0.119	22.0		
CL: Clearance [L/h][b]	0.0200	1.82		
CL: Power of BWT on CL [-][c]	0.728	3.06		
CL: Power of CGFR on CL [-][c]	0.270	6.84		
CL: Power of ALB on CL [-][c]	-0.755	9.50	0.0642	4.18
CL: Power of BSJC on CL [-][c]	0.0783	12.6		
CL: Exponent of NSAID on CL [-][c]	0.0844	15.7		
CL: Exponent of Female Gender on CL [-][c]	-0.0721	20.5		
VP: Peripheral Volume [L][b]	4.02	4.77	0.183	14.7
VP: Power of BWT on VP [-][c]	0.632	7.27		
Q: Intercompartmental Clearance [L/h]	0.0265	9.41	NE	NA
F1: Absolute Bioavailability of SC Formulation [-]	0.823	8.73	0.788	14.4
Proportional Residual Error	NA	NA	0.0552	3.35
Additive Residual Error	NA	NA	0.00165	50.9
Minimum value of the objective function = 60414.981				

[a] Eta shrinkage: ETA CL: 15.5%, ETA VC: 60.3%, ETA VP: 52.3%, ETA KA: 83.0%, ETA F1: 55.6%; Epsilon Shrinkage: Proportional: 13.3%, Additive: 13.3%

[b] $CL_{TV,ref}$, $VC_{TV,ref}$, $VP_{TV,ref}$ are typical values of CL, VC, VP at the reference covariate values. Covariate effects were estimated relative to a reference 50 year patient who is male, weighing 70 kg, with a calculated GFR of 98.66 mL/min/1.73m^2, baseline albumin level of 4.1 g/dL, swollen joint count of 15, not on NSAIDs

[c] $$CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{CL_{BWT}} \times \left(\frac{CGFR_b}{CGFR_{ref}}\right)^{CL_{CGFR}} \times \left(\frac{ALB_b}{ALB_{ref}}\right)^{CL_{ALB}} \times \left(\frac{BSJC_b+1}{BSJC_{ref}+1}\right)^{CL_{SWOL}} \times exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID})$$

$$VC_{TV} = VC_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VC_{BWT}} \times \left(\frac{AGE_b}{AGE_{ref}}\right)^{VC_{AGE}}$$

$$VP_{TV} = VP_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{VP_{BWT}}$$

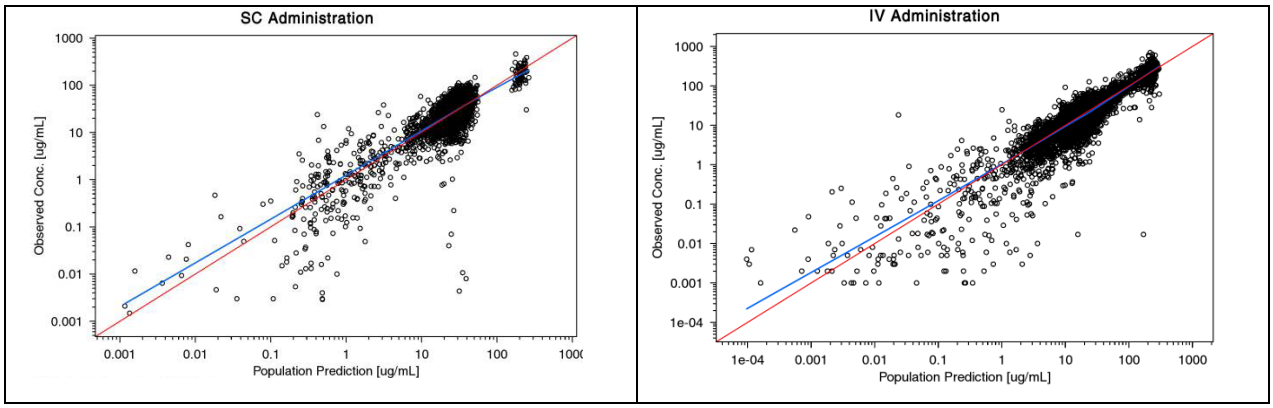
(Source: Table 5.1.1.4-1, pop PK –ER report)

2.1.3.1 Model evaluation

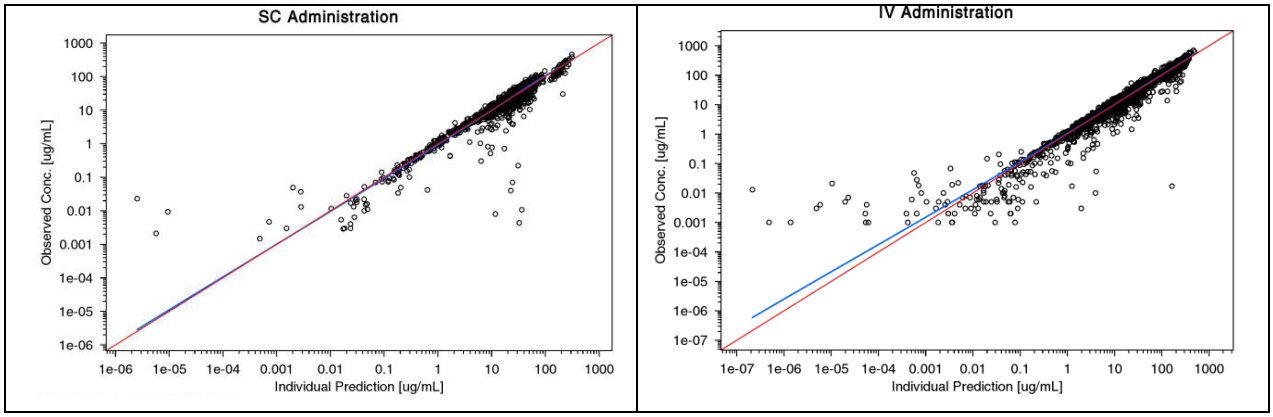
Selected goodness of fit (GOF) plots submitted by the applicant are shown in Figure 12. Applicant has submitted other variations of GOF plots, suggesting adequate model fit.

SC Abatacept:

observations versus population prediction DV vs. PRED



observations versus individual prediction DV vs. IPRED



Conditional weighted residuals versus Time after dose CWRES vs. TAD

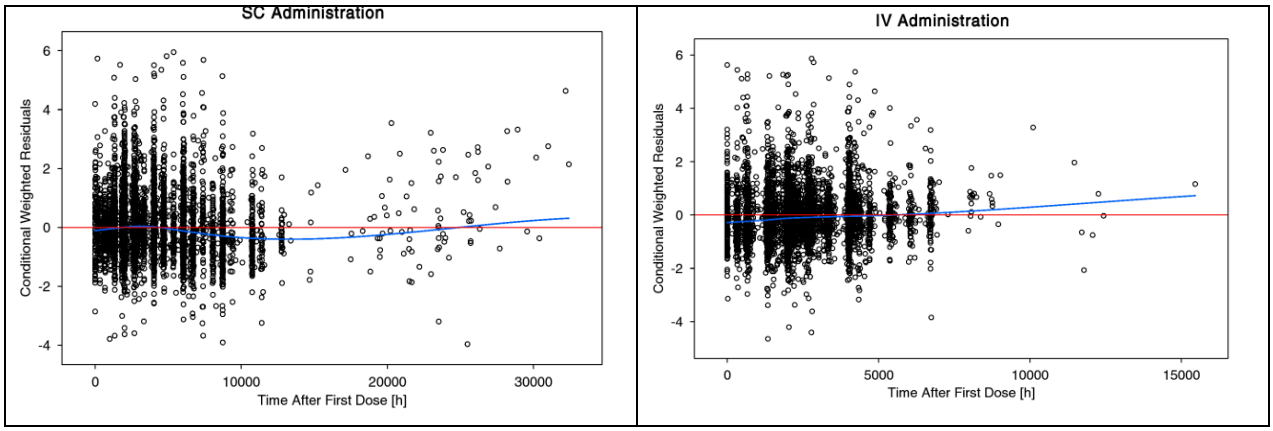


Figure 12. Goodness of fit plot for IV and SC abatacept for final PPK model.

(Source: Figure 5.1.1.4-1, Figure 5.1.1.4-2, Figure 5.1.1.4-3, pop PK-ER report)

Reviewer's comments:

- *A rigorous analysis assessing the of the covariate effects on abatacept exposure was performed using population PK methodology. 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 is 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 6-17 years of age.*

2.1.3.2. Model based estimates of exposure

The following summary measures of individual abatacept exposure were obtained and summarized from the final PK model for each patient: Cminss, Cmaxss, Cavss. These individual abatacept exposure estimates were used in exposure response analysis for efficacy and safety. The simulation based on pop PK model is demonstrated that abatacept exposure with SC dosing regimen is comparable in pediatric PJIA patients vs adult RA patients (Section 1.1.3).

Reviewer's comments:

- *The efficacy of SC abatacept in PJIA was extrapolated from IV abatacept efficacy in PJIA based on observed steady state trough concentration, not the simulated exposure.*
- *The simulated abatacept exposure is consistent with the observed data. The simulation along with the observed abatacept trough concentration supported the body-weight tiered dosing regimen. The SC dosing regimen achieved a range of serum concentrations that is comparable to the adult range and specifically achieving trough concentrations above 10 mcg/mL and at the same time not exceeding the upper limit of the concentrations achieved in adults.*

2.2 E-R analysis for efficacy

Assessment of the relationship between abatacept exposure and efficacy in patients with JIA was performed with respect to efficacy endpoints JIAACR30, JIAACR50, JIAACR70, and JIAACR100 on Day 113.

2.2.1 Data

The E-R analyses of efficacy endpoints, JIAACR30, JIAACR50, JIAACR70, and JIAACR100, on Month 4 (Day 113) after initiation of treatment with abatacept was conducted with data from patients (N = 357) ages 6 to 17 years in JIA Studies IM101033 (Period A [4 months], N = 184) administered 10 mg/kg IV monthly and IM101301 (short-term period [4 months], N = 173) administered weight-tiered SC weekly (10 < 25 kg: 50 mg, 25 < 50 kg: 87.5 mg, and ≥ 50 kg: 125 mg) for whom measures of abatacept exposure were available.

2.2.2 Method

The E-R relationship between abatacept exposure and the probability of achieving ACR Pediatric 30, 50, 70, or 100 response criteria (JIAACR30, JIAACR50, JIAACR70, and JIAACR100) as an ordered categorical efficacy endpoint on Day 113 (Month 4) were described by a proportional odds model and included assessments of the effect of covariates (**Table 18**) on the E-R relationship. Alternative summary measures of exposure (peak serum concentration at steady-state [Cmaxss], Cminss, and time-averaged serum concentration at steady-state [Cavss = AUCss(tau)/tau]) were tested to identify the best summary measure of exposure for prediction of clinical outcome. Four alternative functional forms for the effect of each abatacept exposure on the log-odds of JIAACR responses were evaluated: no effect, linear effect, log linear, and hyperbolic effect.

Table 18. Covariates Tested for E-R Relationship of Efficacy

Covariate Name	Description
Age [yr]	Continuous
Body weight [kg]	Continuous
Sex	Categorical (female vs. male)
Race	Categorical (white vs. non-white)
Route	Categorical (subcutaneous vs. intravenous)
Baseline Concomitant Methotrexate Use	Categorical (yes vs. no)
Baseline Concomitant Corticosteroid Use (STER)	Categorical (yes vs. no)
Baseline Concomitant Non-steroidal Anti-Inflammatory Drug Use (NSAIDs)	Categorical (yes vs. no)
Prior Experience With anti-TNF-α Treatment	Categorical (yes vs. no)
Baseline Tender Joint Count[a]	Continuous
Baseline Swollen Joint Count[a]	Continuous
Baseline C-reactive Protein (CRP)	Continuous
Baseline Physician Global Assessment	Continuous
Baseline Duration of Disease State [yr]	Categorical (≤ 2 years, > 2 to 5 years, > 5 years to 10 years, > 10 years)
JIA Category	Categorical (1 = All Other Subtypes, 4 = Persistent Oligoarthritis, 5 = Systemic Arthritis vs. combined 2 = Polyarticular RF+, 3 = Polyarticular RF-)
Immunogenicity (ADA)	Categorical (positive vs. negative)

[a] In JIA, swollen joint count and tender (pain on motion and/or tenderness) joint count are subset of the count for active joints which is a component for JIAACR response definition.

(Source: Table 4.2.1.2-1, popPK-ER report)

2.2.3 Results

The E-R relationship for JIAACR was best described by a log linear function of Cminss. In the JIAACR model, it was identified that abatacept Cminss (compared to Cmaxss and Cavss) was the best measure of exposure for predicting the JIAACR. No covariates were identified to significantly influence the E-R relationship for JIAACR responses. The final JIAACR model parameter estimates are presented in Table 19.

Final model:

$$log\left[\frac{P(JIAACR30_i)}{1-P(JIAACR30_i)}\right]=AL1 + EFF + ETA(1)$$

$$log\left[\frac{P(JIAACR50_i)}{1-P(JIAACR50_i)}\right]=AL2 + EFF + ETA(1)$$

$$log\left[\frac{P(JIAACR70_i)}{1-P(JIAACR70_i)}\right]=AL3 + EFF + ETA(1)$$

$$log\left[\frac{P(JIAACR100_i)}{1-P(JIAACR100_i)}\right]=AL4 + EFF + ETA(1)$$

EFF=BCONC*(LOG(CMINSS)-LOG(20.23))

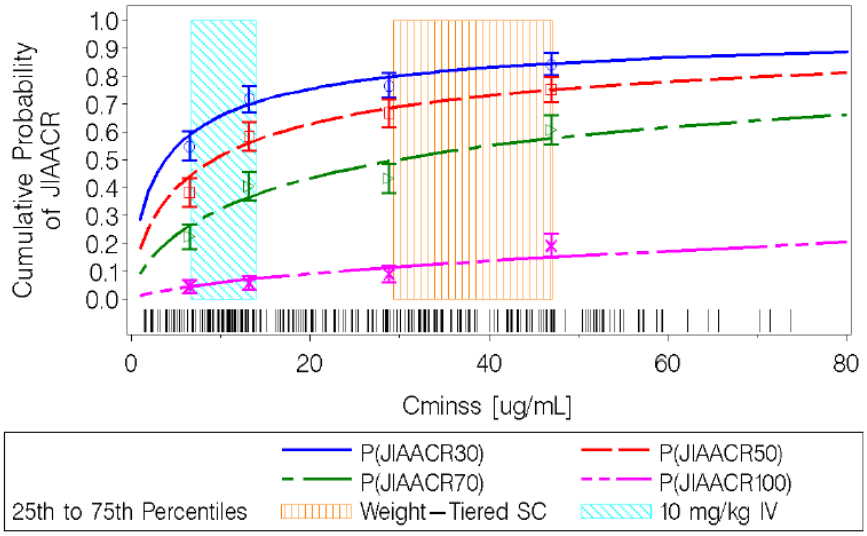
Table 19. Final Model for the Probability of JIAACR Response

	Final Parameter Estimate	
Parameter	**Typical Value**	**%SEM**
AL1: Intercept for JIAACR30 (logit)	1.13	11.2
AL2: Intercept for JIAACR50 (logit)	-0.598	14.3
AL3: Intercept for JIAACR70 (logit)	-0.794	11.6
AL4: Intercept for JIAACR100 (logit)	-2.03	8.78
BCONC: Slope for log(Cminss) (1/[ug/mL])	0.678	16.4

(Source: Table 5.2.1.3-1, pop PK-ER report)

The probability of achieving a JIAACR response (JIAACR30, JIAACR50, JIAACR70, and JIAACR100) at 4 months was found to increase with increasing Cminss (Figure 13). The observed proportions of responders in each quartile of Cminss falls within the prediction interval (data not shown) for each JIAACR response category indicating the data are accurately characterized by the model.

For IV administration of abatacept, Cminss of 10 µg/mL was associated with the near maximal JIAACR30 efficacy response in JIA patients. At the observed range of Cminss for weight-tiered weekly SC administration of abatacept, the probability of JIAACR response was reaching a plateau.



The lines represent the model—based predicted probability of JIAACR responder. The symbols represent the median Cminss of the grouped data and associated observed probabilities. The bars around the symbols represent the standard errors of the observed proportions. The hash marks near the x—axis represent the individual Cminss for JIAACR responders.

Figure 13. Observed and Predicted Probability of JIAACR Response at Month 4 (Study IM101301

and IM101033)
(Source: Figure 5.2.1.3-1, popPK-ER report)

2.3 E-R analysis for safety

Graphical exploratory assessment of the relationship between abatacept exposure and safety was performed in patients with JIA with respect to infection AEs. Other AEs (eg, malignancies, autoimmune disorders, local injection-site reactions, AEs within 24 hours of drug administration) were rare, therefore were not included in the E-R analysis. The PPK model-predicted exposure measures (Cminss, Cmaxss, and Cavss) were used for the E-R analysis of safety.

Except for a higher Cmin, the exposure (AUC and C_{max}) with abatacept SC dosing regimen is much lower compared to those of the abatacept IV dosing regimen (Figure 5). No new safety signals were observed in Study IM101301. These results indicate that SC administration of abatacept causes no unique safety issues in the JIA population relative to the same population treated with IV abatacept or to adults with RA.

Exploratory E-R analysis was performed by graphical examination of the relationship between summary measures of abatacept exposures (Cminss, Cmaxss, and Cavss) and the occurrence of infection adverse events (AEs). Other AEs (eg, malignancies, autoimmune disorders, local injection-site reactions, AEs within 24 hours of drug administration) were rare, and therefore were not included in the E-R analysis.

Based on graphical exploration (Figure 14), there was no relationship between abatacept systemic exposure (Cminss, Cavgss, and Cmaxss) and the incidence of infection within the exposure range tested in the JIA studies. This is consistent with that observed in the adult RA studies for both IV and SC abatacept.

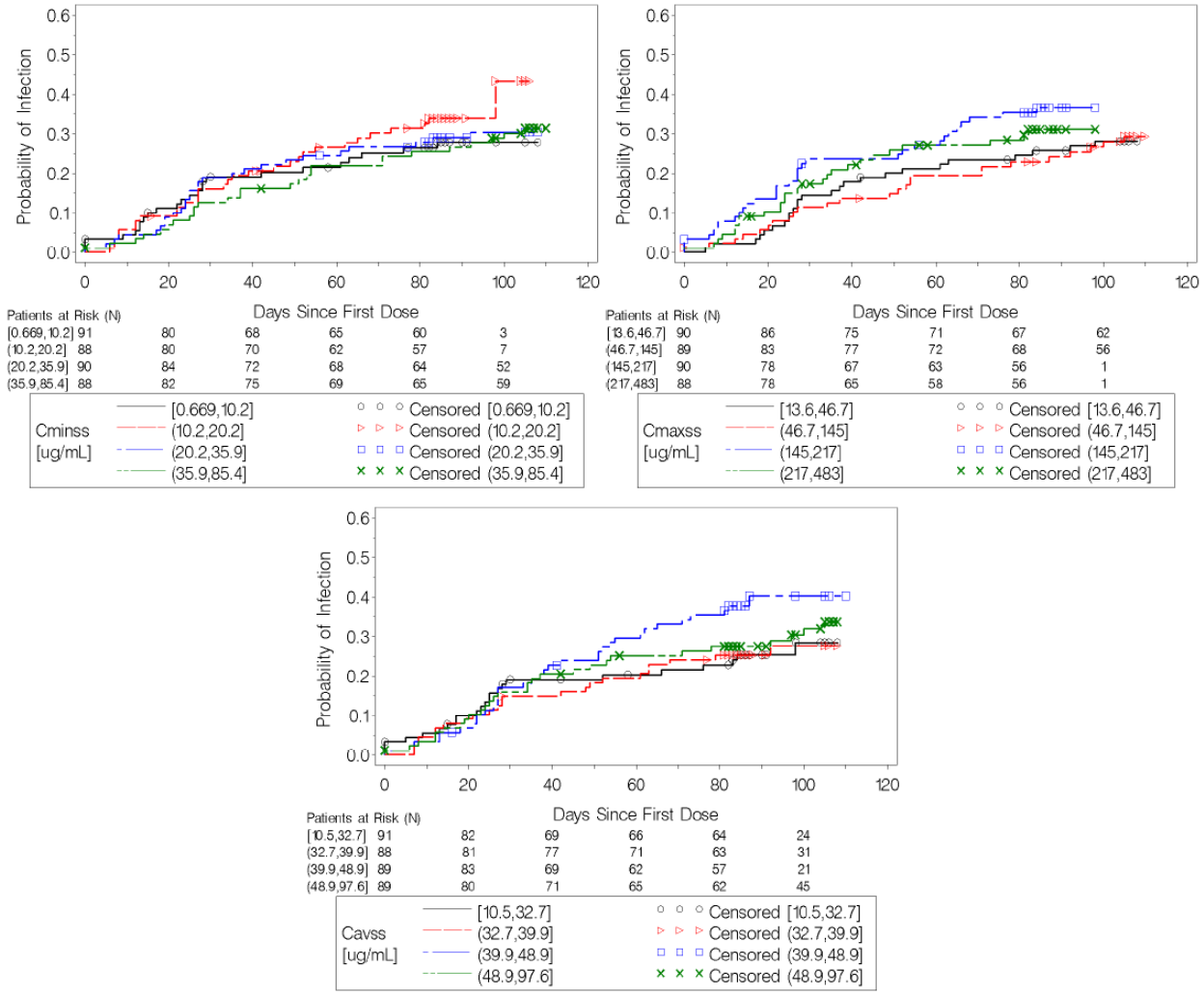


Figure 14. Kaplan-Meier Plots of Probability of First Infection Regardless of Seriousness Versus Days by Quartiles of Abatacept Exposure (IV and SC)

(Source: Figure 7, Summary Clin Pharm)

4.3 Appendix 3 – New Drug Application Filing and Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	125118 (S211)	**SDN**	2074
Applicant	BMS	**Submission Date**	9/30/2016
Generic Name	Abatacept	**Brand Name**	ORENCIA
Drug Class	Selective T cell costimulation modulator		
Indication	PJIA		
Dosage Regimen	10 to< 25 kg, 50 mg QW; 25 to <50 kg, 87.5mg QW; ≥50 kg ,125 mg QW		
Dosage Form	PFS	**Route of Administration**	Subcutaneous
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Jianmeng Chen	Anshu Marathe
Pharmacometrics	Jianmeng Chen	Jingyu (Jerry) Yu
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	11/29/2016	**74-Day Letter Date**	12/13/2016
Review Due Date	3/8/2017	**PDUFA Goal Date**	3/30/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

OSI inspection will be requested for bioanalytical report K004 (Part A of study VX13-

809-11) and L236 (Part B of study VX13-809-11).

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	IM101301
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		1	IM101301

☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	1	Integrated pharmacometric analysis report (Pop PK and ER)
☑ Exposure-Efficacy	1	
☑ Exposure-Safety	1	

Total Number of Studies and reports	**In Vitro**		**In Vivo**	2
Total Number of Studies/reports to be Reviewed				2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
03/08/2017

JINGYU YU
03/08/2017

ANSHU MARATHE
03/08/2017