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**Clinical Pharmacology and Biopharmaceutics  
Review**



**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
**Public Health Service**

**Memorandum**

**Food and Drug Administration**  
**Center for Drugs Evaluation and Research**  
**1451 Rockville Pike**  
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**CLINICAL PHARMACOLOGY REVIEW**

Date: June 17, 2005

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Subject: Clinical Pharmacology Review of Biologic License Application STN 125118 for Bristol-Myers Squibb Company's Abatecept (ORENCIA™)

To: Center / Division / Office – CDER / ODE VI / DTBIMP  
Primary Reviewer – Keith Hull, M.D.

Please see the attached review.

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## INTRODUCTION

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.

Abatacept selectively modulates a costimulatory signal required for full activation of T lymphocytes expressing CD28. T lymphocytes are found in the synovium of patients with rheumatoid arthritis (RA). Activated T lymphocytes contribute to the pathogenesis of RA and other autoimmune diseases. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, costimulatory signal. A major costimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept binds specifically to CD80 and CD86 selectively inhibiting this co-stimulatory pathway. Studies suggest that naive T lymphocyte responses are more affected by abatacept than memory T lymphocyte responses.

The proposed indication is "...for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, including TNF blocking agents. [Abatacept] may be used in combination with methotrexate or other non-biologic DMARD therapy."

The proposed dose of abatacept is a fixed dose IV infusion over 30 minutes, in dose tiers by body weight, to be given at 2 and 4 weeks after the first infusion, then once a month thereafter. The proposed doses in the body weight tiers approximate a dose of 10 mg/kg. Subjects weighing < 60 kg received 500 mg, subjects weighing between 60 kg to 100 kg received 750 mg, and subjects weighing > 100 kg received 1000 mg of abatacept.

The pharmacokinetic (PK) information for intravenously (IV) and subcutaneously (SC) administered abatacept was derived from 247 subjects in a total of nine Phase 1 and Phase 2 clinical studies. PK results were derived by non-compartmental analysis.

There were four Phase I studies. Three of the four Phase I studies were carried out in subjects with psoriasis vulgaris, and one study was carried out in healthy subjects. Of the three Phase I studies in psoriasis subjects, two were single dose escalating studies where abatacept was administered either IV (IM101003; N = 24) or SC (IM101004; N = 30) at doses ranging from 1 to 8 mg/kg. The third Phase 1 study in psoriasis subjects (IM101001; N = 43) was a multiple dose escalating study where abatacept was administered IV at doses ranging from 0.5 to 50 mg/kg. The Phase 1 healthy subject study, IM101017 (N = 28), was a comparative PK study at 10 mg/kg initiated prior to the start of the Phase 3 program to assess the effect on PK of modifications made to the manufacturing process of abatacept (between Phase 2 and Phase 3).

There were five Phase 2 studies where the non-compartmental PK of abatacept was evaluated: a multiple dose study (IM101005; N = 51) in subjects with psoriasis who were administered abatacept IV at doses ranging from 8 to 25 mg/kg, three studies in subjects with rheumatoid arthritis (RA), IM103002 (N = 8), IM101100 (N = 29), and IM101101 (N = 6), and one study in subjects with relapsing-remitting multiple sclerosis (MS) (IM101200; N = 28). Study

IM103002 was an exploratory dose ranging study where multiple IV doses of 0.5, 2.0, and 10 mg/kg of abatacept were evaluated as monotherapy in RA subjects. In the other two Phase 2 RA studies, IM101100 and IM101101, the PK data for IV administered abatacept were obtained at doses of 2 and 10 mg/kg (IM101100) and at 2 mg/kg (IM101101). The PK portions of the latter two studies were carried out as site-specific PK sub-studies of the main protocols. In study IM101100, abatacept was administered to RA subjects in combination with methotrexate, and in study IM101101, abatacept was administered to RA subjects in combination with etanercept. In the Phase 2 multiple dose study in MS subjects (IM101200), abatacept was administered at 2 and 10 mg/kg as a single agent.

PK data were also obtained from 150 randomly selected subjects (50 subjects from each of the three Phase 3 RA studies, IM101102, IM101029, and IM101031). The PK results from the 150 randomly selected Phase 3 subjects and data from the Phase 2 RA studies, form the basis of the population pharmacokinetic (POPPK) analysis that was carried out in support of the abatacept development program. In these Phase 3 studies, abatacept was administered intravenously at a fixed dose approximating 10 mg/kg based upon weight. Thus, subjects weighing < 60 kg received 500 mg, subjects weighing between 60 kg to 100 kg received 750 mg, and subjects weighing > 100 kg received 1000 mg of abatacept. Infusions of abatacept were given over approximately 30 minutes. Following the initial administration, abatacept was administered at 2 and 4 weeks after the first infusion, then once a month thereafter.

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**Summary of Studies/Analyses**

A summary of the studies contributing to the PK of abatacept is shown in the table below:

Summary of Studies					
Study Category	Study	Process*	Dose	Duration of Study	No. Subjects contributing to PK data
<b>Phase 1</b>					
Healthy subjects	IM101017	D, E	10 mg/kg IV X 1	1 dose	28
Psoriasis subjects	IM101003	A	1, 2, 4, and 8 mg/kg IV X 1	1 dose	24
Psoriasis subjects	IM101004	A, B	Part 1: 1, 2, and 4 mg/kg SC X 1 Part 2: 4 and 8 mg/kg SC X 1	1 dose	18 12
Psoriasis subjects	IM101001	A	0.5, 1, 2, 4, 8, 16, 25, and 50 mg/kg IV on days 1, 3, 16, and 29	14 wks	43
<b>Phase 2</b>					
Psoriasis subjects	IM101005	A, B	7 treatment arms consisting of a combination of three dose levels (8, 16, and 25 mg/kg or placebo), IV infusions, and two schedules of dosing (12 and 8 infusions)	36 wks	51
RA subjects	IM103002	D	0.5, 2, and 10 mg/kg IV on days 1, 15, 29, and 57	26 wks	8
RA subjects	IM101100	D	2 and 10 mg/kg IV on days 1, 15, 30, and every 30 days thereafter	26 wks	29
RA subjects	IM101101	D	2 mg/kg IV on days 1, 15, 30, and every 30 days thereafter	26 wks	6
MS subjects	IM101200	D, E	2 and 10 mg/kg IV on days 1, 15, 29, and every 28 days thereafter through day 197	26 wks	28
<b>Phase 3</b>					
RA subjects	IM101012	E	500, 750, and 1000 mg based on body weight IV infusions on days 1, 15, and 29, and every 28 days thereafter	52 wks	50
RA subjects	IM101029	E	500, 750, and 1000 mg based on body weight IV infusions on days 1, 15, and 29, and every 28 days thereafter	26 wks	50
RA subjects	IM101031	E	500, 750, and 1000 mg based on body weight IV infusions on days 1, 15, and 29, and every 28 days thereafter	52 wks	50

Comparisons and Analyses Across Studies		
Analysis	Studies From Which Data Collected	No. Subjects contributing to PK data
Population PK Analysis	3 Phase 2 RA studies (IM103002, IM101100, and IM101101) 3 Phase 3 RA studies (IM101102, IM101029, and IM101031)	193
Drug Interactions: Effect of MTX and Etanercept	2 Phase 2 RA Studies (IM101100, and IM101101) 1 Phase 2 MS Study (IM101200)	63

**SYNOPSIS****SINGLE DOSE STUDIES****Study IM101017**

Study to Compare the Pharmacokinetics of CD-CHO1 Process (Process E) Abatacept (BMS-188667) to DE Process (Process D) Abatacept in Healthy Subjects

**Methods**

A single site, randomized, single-dose, parallel group study was used to evaluate the pharmacokinetics of abatacept manufactured by either Process E or Process D in healthy subjects. Thirty (30) subjects were admitted to the clinical study unit and randomized in a 1:1 ratio to receive either abatacept manufactured by Process E or Process D as a single intravenous infusion of 10 mg/kg over 30 minutes. Blood samples were collected at specified time points after dosing for up to 71 days for quantitation of abatacept.

Serum samples were analyzed for abatacept by a validated ELISA method. The standard curve range, prepared in 10% human serum, was from 0.1 to 3.0 ng/mL. This results in a standard curve range of 1 to 30 ng/mL in 100% human serum, defining the lower (LLQ) and the upper limit of quantitation (ULQ), respectively.

Serum samples for pharmacokinetics were obtained on day 1 (at 0, 0.25, 0.5, 1, 2, 6, and 12 hours), and on days 2, 4, 8, 15, 22, 29, 43, 57, and 71. The serum concentration versus time data for abatacept derived from subjects in the study were analyzed by non-compartmental methods.

For  $C_{max}$ ,  $AUC_{\infty}$ , and  $AUC_{0-t}$  of abatacept, 90% confidence intervals for the ratios of population geometric means for the Process E to the Process D were calculated from the results of an analysis of variance on  $\log(C_{max})$ ,  $\log(AUC_{\infty})$ , and  $\log(AUC_{0-t})$ . Summary statistics by manufacturing process were tabulated for other pharmacokinetic parameters.

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## Results

### Pharmacokinetic Results:

Summary statistics for abatacept pharmacokinetic parameters by treatment are presented below.

Formulation	Abatacept Pharmacokinetic Parameters (Study IM101017)					
	C <sub>max</sub> [µg/mL] GM (CV%)	AUC <sub>∞</sub> [µg-h/mL] GM (CV%)	CL [mL/h/kg] Mean (SD)	V <sub>ss</sub> [L/kg] Mean (SD)	T <sub>max</sub> [h] Median (Range)	t <sub>1/2</sub> [Days] Mean (SD)
Process D (n=15)	271.48 (14%)	43758.15 (17%)	0.23 (0.06)	0.10 (0.02)	1.00 (0.50, 6.00)	16.82 (4.50)
Process E (n=13)*	284.71 (23%)	44403.04 (18%)	0.23 (0.04)	0.09 (0.02)	0.50 (0.50, 2.00)	16.68 (3.24)

GM: Geometric Mean

\*Two subjects dosed with Process E were excluded from the analysis of PK parameters and subsequent statistical analysis. Subject IM101017-1-5 was excluded because of possible blood loss during surgery for laparoscopic repair of a perforated duodenal ulcer. Subject IM101017-1-25 was excluded because of a malfunction of the infusion apparatus during drug administration that resulted in the subject receiving an incomplete dose. Therefore, PK parameters were obtained from 15 subjects dosed with Process D and 13 subjects dosed with Process E.

(The values in the table above were taken from page 56 of the Clinical Study Report for IM101017.)

The results above indicate that the mean t<sub>1/2</sub> for abatacept manufactured by either process was similar and was approximately 17 days. Both clearance and volume of distribution were also similar between the two processes.

### Statistical Analysis:

Analysis of variance (ANOVA) results for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>∞</sub> are presented below.

Statistical Analysis for Study IM101017					
Pharmacokinetic Parameter	Adjusted Geometric Mean		Ratio of Geometric Mean		
	Treatment	Geometric Mean	Ratio	Point Estimate	90% Confidence Interval
C <sub>max</sub> [µg/mL]	Process D	271.5	E vs. D	1.05	0.93 to 1.18
	Process E	284.7			
AUC <sub>0-t</sub> [µg-h/mL]	Process D	41788.6	E vs. D	1.022	0.91 to 1.15
	Process E	42698.9			
AUC <sub>∞</sub> [µg-h/mL]	Process D	43758.2	E vs. D	1.015	0.90 to 1.15
	Process E	44403.0			

Abatacept was administered as a single IV infusion of 10 mg/kg over 30 minutes.

(Values corresponding to C<sub>max</sub> in the table above were taken from page 56 of the Clinical Study Report for IM101017.)

(Values corresponding to AUC<sub>0-t</sub> and AUC<sub>∞</sub> in the table above were taken from page 7 of the report entitled "Response to Question Received 06 JUN 2005".)

The geometric mean values for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>∞</sub> were similar between Process D and Process E abatacept (see table above). The 90% confidence intervals for the geometric mean ratio for C<sub>max</sub>, AUC<sub>0-t</sub>, and AUC<sub>∞</sub>, Process E versus Process D, fell within the 80% to 125% equivalence window (see table above).

**Conclusions**

- (1) Single dose pharmacokinetics of Process D and Process E abatacept were comparable based on  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{\infty}$  after an IV infusion of 10 mg/kg in healthy subjects.
- (2) The serum elimination half-life values for Process D and Process E abatacept were similar in healthy subjects given a single IV infusion of 10 mg/kg. The serum elimination half-life was approximately 17 days.
- (3)  $V_{ss}$  values after a single IV infusion of 10 mg/kg over 30 minutes in healthy subjects approximated plasma volume, indicating that abatacept was confined primarily to the vascular system, and did not significantly distribute into extravascular spaces.

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**Study IM101003**

A Phase I, Randomized, Double-blind, Placebo-controlled Study to Assess the Pharmacokinetics, Immunogenicity, and Safety of Escalating Doses of Abatacept (BMS-188667) Given as a Single Intravenous Infusion to Patients With Psoriasis Vulgaris

**Methods**

This was a randomized, double-blind, placebo-controlled, sequential ascending-dose study of abatacept. Four abatacept doses were studied: 1, 2, 4, and 8 mg/kg. A total of 32 subjects were enrolled in cohorts of 8 at each of the 4 dose levels. For each cohort, and at each dose level, subjects were randomized in a double-blind fashion, with 6 subjects receiving 1-hour infusions of abatacept, and 2 subjects receiving placebo.

No subject received more than a single dose of either abatacept or placebo. Abatacept was manufactured by Process A and supplied in individual vials containing 50 mg of abatacept.

Abatacept levels in serum were assayed by a sensitive ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL.

PK samples were obtained at day 1, 2, 3, 8, 15, 22, 29, 26, and 43 for all subjects. The 4 and 8 mg/kg cohorts also got PK samples at 60, 90, and 120 days. The PK parameters were derived from non-compartmental analysis.

**Results****Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters are presented below.

Mean (SD) Pharmacokinetic Parameter Values for Abatacept (Study IM101003; N=24)						
Dose [mg/kg]	C <sub>max</sub> [µg/mL]	T <sub>max</sub> * [h]	AUC <sub>∞</sub> [µg-h/mL]	t <sub>1/2</sub> [h]	CL <sub>t</sub> [mL/h/kg]	V <sub>ss</sub> [mL/kg]
1.0	31.7 (5.1)	1.0 (1.0-2.0)	5455 (593)	395 (114)	0.186 (0.023)	84.7 (17.6)
2.0	53.3 (11.0)	1.5 (1.0-4.0)	9897 (1508)	388 (76)	0.200 (0.036)	89.0 (12.1)
4.0	147 (26.4)	1.5 (1.0-2.0)	26108 (2458)	346 (99)	0.155 (0.155)	70.9 (14.2)
8.0	312 (67.5)	1.0 (1.0-4.0)	48968 (4003)	346 (78)	0.166 (0.014)	77.2 (4.6)

\* Median (Range)

(The values in the table above were taken from page 38 of the Clinical Study Report for IM101003.)

As dose levels increased in the ratio of 1: 2: 4: 8, the mean C<sub>max</sub> and AUC<sub>∞</sub> values increased in the ratios of 1: 1.7: 4.6: 9.8 and 1: 1.8: 4.8: 9.2, respectively. These results indicated that both C<sub>max</sub> and AUC(INF) are approximately proportional to dose.

The mean t<sub>1/2</sub> values ranged between 14.4 to 16.5 days and did not appear to change with increasing doses of abatacept. The mean weight-adjusted clearance (CL<sub>t</sub>) values ranged from 0.16 to 0.20 mL/h/kg and did not appear to change with increasing doses of abatacept. The mean V<sub>ss</sub> values ranged from 0.07 to 0.09 L/kg and did not appear to change with increasing doses of abatacept.

**Conclusions**

- (1) Following IV administration, abatacept exhibited nearly linear pharmacokinetics over the dose range studied (1.0 to 8.0 mg/kg) in psoriasis subjects.
- (2) Mean  $t_{1/2}$  values ranged between 14.4 to 16.5 days and did not appear to change with increasing doses of abatacept in psoriasis subjects.
- (3) Mean weight-adjusted CL values and mean Vss values did not appear to change with increasing doses of abatacept in psoriasis subjects.
- (4) Vss values approximated plasma volume, indicating that abatacept was confined primarily to the vascular system, and did not significantly distribute into extravascular spaces.

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## **Study IM101004**

A Phase 1, Open Label Study To Assess The Safety, Pharmacokinetics And Immunogenicity Of Escalating Single Doses Of BMS-188667 Followed By A Randomized, Double-Blind, Placebo-Controlled Assessment Of The Bioactivity Of BMS-188667 Administered Subcutaneously To Patients With Psoriasis Vulgaris

### **Methods**

Part 1 of this study was a non-randomized, ascending, single dose, open label study with 18 subjects (6 subjects per dose level) who were administered abatacept (50-mg/vial Process A formulation) SC at doses of 1, 2, and 4 mg/kg.

Part 2 of the study was a randomized, double-blind, placebo-controlled stage with 27 subjects (6 active, 3 placebo per dose level) who were administered abatacept (200 mg/vial Process B formulation) SC at doses of 4, 8, and 16 mg/kg. However, because of reported incidences of irritation (Grade 1 redness, burning, and/or swelling) at the injection site by subjects following SC administration at all doses through 8 mg/kg, the study was terminated prior to the enrollment of subjects into the highest dose group of 16 mg/kg. A total of 18 subjects (12 active, 6 placebo) were enrolled in Part 2 of the study.

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. Serum samples for pharmacokinetics were obtained on day 1 (at 0, 0.25, 0.5, 1, 2, 4, 8, 12, and 18 hours), and on days 2, 3, 5, 6, 7, 8, 15, 22, 29, 36, 43, 60, 90, and 120. The PK parameters were derived from non-compartmental analysis.

### **Results**

#### **Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters are presented below.

Mean (SD) PK Parameter Values for Single Dose Subcutaneously Administered Abatacept (Study IM101004; N=30)						
Dose [mg/kg]	C <sub>max</sub> [µg/mL]	T <sub>max</sub> <sup>#</sup> [h]	AUC <sub>∞</sub> [µg-h/mL]	t <sub>1/2</sub> [days]	CL <sub>T</sub> /F [mL/h/kg]	V <sub>ss</sub> /F [mL/kg]
1.0 (n=6)*	9.8 (1.2)	108 (48-168)	4483 (886)	8.7 (3.4)	0.23 (0.04)	0.07 (0.03)
2.0 (n=6)*	13.8 (4.3)	96 (72-120)	7143 (2081)	9.6 (4.1)	0.31 (0.11)	0.09 (0.03)
4.0 (n=6)*	43.4 (8.0)	84 (48-144)	19268 (4467)	10.4 (3.2)	0.22 (0.04)	0.08 (0.02)
4.0 (n=6)**	41.1 (9.7)	72 (48-96)	18761 (4836)	12.0 (3.5)	0.23 (0.07)	0.09 (0.02)
8.0 (n=6)**	60.2 (8.4)	84 (8-120)	29956 (5995)	13.0 (3.9)	0.28 (0.05)	0.12 (0.02)

\* 50 mg/vial formulation

\*\* 200 mg/vial formulation

# Median (Range)

(The values for T<sub>max</sub> in the table above were taken from page 43 of the Clinical Study Report for IM101004.)

(The values for the other PK parameters in the table above were taken from page 41 of the Summary of Clinical Pharmacology Studies.)

Increases in the mean  $C_{max}$  and  $AUC_{\infty}$  values appear to be slightly less than dose proportional. As the dose of abatacept increased in the ratio of 1: 2: 4: 8, the mean  $C_{max}$  values increased in the ratio of 1: 1.4: 4.3: 6.2, and the mean  $AUC_{\infty}$  values increased in the ratio of 1: 1.6: 4.2: 6.7. There was no apparent relation of  $t_{1/2}$  value with increasing dose. Mean  $t_{1/2}$  value ranged from 9 to 13 days. The weight-adjusted  $CL_T/F$  and  $V_{ss}/F$  values appeared to be independent of dose. The median  $T_{max}$  values for abatacept after SC administration ranged from 3 to 4.5 days.

### **Conclusions**

- (1) Following SC administration, abatacept exhibited nearly linear pharmacokinetics over the dose range studied (1.0 to 8.0 mg/kg) in psoriasis subjects.
- (2) Median  $T_{max}$  values for abatacept after SC administration ranged from 3 to 4.5 days in psoriasis subjects.
- (3) Mean  $t_{1/2}$  values for abatacept after SC administration ranged from 9 to 13 days in psoriasis subjects, and did not appear to change with increasing doses of abatacept.
- (4) Mean weight-adjusted  $CL_T/F$  values and mean  $V_{ss}/F$  values after SC administration did not appear to change with increasing doses of abatacept in psoriasis subjects.
- (5)  $V_{ss}$  values approximated plasma volume, indicating that abatacept was confined primarily to the vascular system, and did not significantly distribute into extravascular spaces.

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**MULTIPLE DOSE STUDIES****Study IM101001**

Phase 1 Study of BMS-188667 (CTLA4Ig) In Patients With Psoriasis Vulgaris.

**Methods**

This was a multi-center, open-label, dose escalation trial. Subjects were administered abatacept as 4 one-hour IV infusions on Days 1, 3, 16, and 29. Abatacept was manufactured by Process A and supplied in individual vials containing 50 mg of abatacept. Eight dose levels were evaluated: 0.5, 1, 2, 4, 8, 16, 25, and 50 mg/kg. Of the 45 subjects who were enrolled into the study, 43 were treated with abatacept and contributed to the PK of the drug. The number of subjects ranged between 4 to 6 per dose level for the evaluation of PK.

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. PK samples were obtained on day 1 (0, 0.5, 1, 2, 4, and 6 hours), day 2 (0 hours), day 3 (0 and 1 hours), day 8 (0 hours), day 16 (1 hour), day 17 (0 hours), day 29 (0, 0.5, 1, 2, 4, and 6 hours), day 30, day 36, day 43, day 50, day 57, day 64, day 78, day 99, day 120, day 148, and day 176.

C<sub>max</sub>, T<sub>max</sub>, AUC(24), and t<sub>1/2</sub> were determined after the first and last dose. AUC(1176) was determined after the last dose. AUC(24) is the area under the serum concentration versus time curve from time zero (time of dose) to 24 hours. AUC(24) was chosen for comparison between dose levels and between first dose and last dose because it served as a common sampling point. AUC(1176) is the area under the serum concentration versus time curve from time of last dose to 1176 hours. PK parameters were derived from non-compartmental analysis.

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## Results

### Pharmacokinetic Results:

Summary statistics for abatacept pharmacokinetic parameters after the first and last dose are presented below.

Mean (SD) PK Parameter Values for Abatacept (Study IM101001)							
Dose Level [mg/kg]	Cmax [µg/mL]		AUC (0-24) [µg-h/mL]		t <sub>1/2</sub> [days]	AUC (0-1176) [µg-h/mL]	Accumulation Index*
	First Dose	Last Dose	First Dose	Last Dose			
0.5 (N=4)	12.8 (3.3)	17.0 (4.6)	210 (55)	313 (78)	9.8 (4.1)	5761 (3621)	1.49
1 (N=5)	22.4 (4.2)	29.9 (6.8)	389 (83)	595 (116)	14.8 (7.7)	8805 (1532)	1.53
2 (N=5)	59.2 (12.3)	73.1 (12.3)	1048 (183)	1462 (332)	13.6 (6.3)	18374 (5249)	1.39
4 (N=5)	101 (20)	155 (22)	1699 (412)	2967 (363)	18.8 (9.0)	43003 (13974)	1.75
8 (N=6)	208 (25)	323 (62)	3717 (432)	6188 (1006)	14.9 (5.8)	75441 (13095)	1.66
16 (N=6)	585 (142)	783 (163)	9203 (2211)	14749 (4583)	10.8 (5.1)	164810 (52687)	1.60
25 (N=6)	1097 (239)	1312 (274)	16766 (3036)	24736 (2039)	15.5 (4.1)	328163 (52774)	1.48
50 (N=6)	1571 (312)	2201 (578)	27433 (4197)	37070 (9398)	18.3 (6.4)	461930 (97186)	1.35

\* Accumulation Index = AUC(0-24) Last Dose / AUC (0-24) First Dose

One-hour IV infusions of abatacept were administered on Days 1, 3, 16, and 29.

[AUC(0-1176) values in the table above were taken from pages 168 to 175 of the IM101001 Clinical Study Report.]

[Values for other PK parameters in the table above were taken from page 95 of the IM101001 Clinical Study Report.]

As the dose levels increased in the ratios of 1: 2: 4: 8: 16: 32: 50: 100, the mean C<sub>max</sub> values after the first dose on Day 1 increased in the ratio of 1: 1.7: 4.6: 7.8: 16.2: 45.6: 85.4: 122.4. Similarly, the mean AUC(0-24 hours) values after the first dose on Day 1 increased in the ratio of 1:1.8: 5.0: 8.1: 17.7: 43.8: 79.8: 130.5. Thus, mean C<sub>max</sub> and AUC(0-24 hours) values increased in proportion with the dose increment at the lower dose levels (0.5-8 mg/kg), and were slightly greater than dose proportional at higher dose levels (16-50 mg/kg).

As the dose levels increased in the ratios of 1: 2: 4: 8: 16: 32: 50: 100, the mean C<sub>max</sub> values after the last dose on Day 29 increased in the ratio of 1: 1.8: 4.3: 9.1: 19.0: 46.0: 77.2: 129.5. Similarly, the mean AUC(0-24 hours) values after the last dose on Day 29 increased in the ratio of 1:1.9: 4.7: 9.5: 19.8: 47.1: 79.0: 118.4. Thus, the ratio of increases by dose levels for the mean C<sub>max</sub> and AUC(0-24 hours) values after the last dose were similar to the ratio of increase by dose levels for the mean C<sub>max</sub> and AUC(0-24 hours) values obtained after the first dose.

As the dose levels increased in the ratios of 1: 2: 4: 8: 16: 32: 50: 100, the mean AUC(0-1176 hours) values after the last dose on Day 29 increased in the ratio of 1: 1.5: 3.2: 7.5: 13.1: 28.6: 57.0: 80.2. Thus, mean AUC(0-1176 hours) values appear to be slightly less than dose proportional through the dose range of 0.5 to 50 mg/kg.

The mean t<sub>1/2</sub> values after the last dose ranged from 9.8 to 18.3 days and did not appear to change with increasing doses of abatacept.

Following multiple dosing, the accumulation index, calculated as the ratio of mean AUC(0-24 hours) values for the last dose to mean AUC(0-24 hours) after the first dose, was consistent



across dose levels and ranged from 1.4 to 1.8, indicating minimal accumulation following this multiple dose regimen.

### **Conclusions**

- (1) Following a multiple dose regimen of IV administration (Days 1, 3, 16, and 29), abatacept exhibited nearly linear pharmacokinetics over the dose range studied (0.5 to 50 mg/kg) in psoriasis subjects.
- (2) Mean C<sub>max</sub> after the first dose, AUC(0-24 hours) after the first dose, C<sub>max</sub> after the last dose, AUC(0-24 hours) after the last dose, and AUC(0-1176 hours) after the last dose increased over the dose range studied (0.5 to 50 mg/kg) in a manner that was approximately dose proportional in psoriasis subjects.
- (3) Mean  $t_{1/2}$  values for abatacept after the last dose IV administration ranged from 9 to 13 days in psoriasis subjects, and did not appear to change with increasing doses over the dose range studied (0.5 to 50 mg/kg).
- (4) The ratio of mean AUC(0-24 hours) values for the last dose to mean AUC(0-24 hours) after the first dose, was consistent across the dose range studied (0.5 to 50 mg/kg) and ranged from 1.4 to 1.8, indicating minimal accumulation following a multiple dose regimen of IV administration (Days 1, 3, 16, and 29) of abatacept in psoriasis subjects.

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**Study IM101005**

Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of BMS-188667 (CTLA4Ig) in Patients with Psoriasis Vulgaris

**Methods**

This study was a multi-center, randomized, double-blind, placebo-controlled trial in subjects with psoriasis vulgaris. Seven treatment arms consisting of a combination of three BMS-188667 (CTLA4Ig) dose levels (8.0, 16.0 and 25.0 mg/kg) or placebo and two schedules of administration (12 and 8 intravenous infusions, respectively) were to be explored within this study. Unit doses of 16.0 mg/kg were explored only within the 8 intravenous infusion treatment arm (Schedule 2).

A total of 144 subjects were to be randomized asymmetrically to the five active treatment arms (120 subjects total) and the two placebo arms (24 subjects total). Subjects receiving fewer than five infusions of study medication were to be followed through at least Week 13 (Day 85). Subjects receiving five or more study treatment infusions were to be followed through the end of study, Week 36 (Day 246).

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. Blood samples for pharmacokinetic analysis were to be obtained in study subjects at Days 1 (0, 0.5, 1, 2, and 6 hours), 3 (0 and 1 hour), 15 (0 and 1 hour), 43 (0 and 1 hour), 71 (0 and 1 hour), 85, 113, 134, 162, 190, 218 and 246. PK parameters were derived from non-compartmental analysis.

**Results**

Though a total of 144 subjects were expected to participate in the study, the study was terminated early because of peri-infusional adverse events associated with the infusion of abatacept. Extensive characterization of the drug substance led to the discovery that the adverse events may have been due to a biologically active protein [ ] that had co-purified with abatacept. Though IM101005 was intended to be a multiple dose, dose escalation study, early termination of the study resulted in the PK being evaluated only after the first dose. Seventy subjects registered and signed informed consent; 65 subjects received one or more infusions of study medication.

Due to the suspension of dosing in this study, and because only seven subjects completed the established course of therapy, no pharmacokinetic analysis was performed at times other than the first 48 hours of dosing on this study. The pharmacokinetic variables of serum elimination half-life ( $t_{1/2}$ ), total clearance ( $CL_T$ ) and apparent volume of distribution ( $V_d$ ) could not be determined accurately for abatacept due to the long elimination phase of the compound and the fact that PK samples through 48 hours only were included in the analyses.

**Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters are presented below.

Treatment Dose <sup>a</sup> [mg/kg]	Treatment Schedule <sup>b</sup>	Mean (SD) PK Parameter Values of Abatacept <sup>c</sup>	
		Cmax [µg/mL]	AUC (0-48 h) [µg-h/mL]
8 (N=13)	1	246 (45.3)	6021 (1155)
8 (N=11)	2	263 (58.7)	7173 (2262)
16 (N=10)	2	758 (160)	16607 (3425)
25 (N=9)	1	923 (108)	23850 (4088)
25 (N=8)	2	1027 (266)	25373 (6820)

a. Seven treatment arms consisting of a combination of 3 abatacept dose levels, 8, 16, and 25 mg/kg or placebo and 2 schedules of administration (12 and 8 intravenous infusions)

b. Schedule 1 = 12 doses; Schedule 2 = 8 doses

c. The mean PK parameters were obtained from the serum concentration versus time data for 51 subjects following the administration of abatacept on Day 1.

(Values in the table above are taken from Page 42 of the Clinical Pharmacology Summary.)

Since the dosing period from Day 1 to Day 3 is the same for both dosing schedules, individual Cmax and AUC(48) values for each dose level were grouped together to examine dose proportionality and linearity. See table below.

Treatment Dose [mg/kg]	Treatment Schedule	Mean (SD) PK Parameter Values of Abatacept	
		Cmax [µg/mL]	AUC (0-48 h) [µg-h/mL]
8 (N=24)	1,2	254 (51.4)	6625 (1872)
16 (N=10)	2	758 (160)	16607 (3425)
25 (N=17)	1,2	972 (199)	24394 (5017)

(Values in the table above are taken from Page 42 of the Clinical Pharmacology Summary.)

As the doses of abatacept increased in the ratios of 1:2:3.1, mean Cmax values following dosing on Day 1 increased in the ratios of 1:3:3.8 and mean AUC(48) values increased in the ratios of 1:2.5:3.7. Thus, increases in mean Cmax and AUC(48) values appeared to be slightly greater than dose proportional.

**Conclusions**

- (1) Following IV administration, abatacept exhibited nearly linear pharmacokinetics over the dose range studied (8.0 to 25.0 mg/kg) in psoriasis subjects.

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**Study IM103002**

A Pilot, Multi-Center, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Safety, Preliminary Clinical Activity and Immunogenicity of Multiple Doses of BMS-188667 and BMS-224818 Administered Intravenously to Subjects with Rheumatoid Arthritis

**Methods**

This was a randomized, double-blind, placebo controlled, parallel and multiple dose study in 214 subjects with RA who had failed at least one Disease Modifying Anti-Rheumatic Drug (DMARD) or etanercept. Eligible subjects had all DMARDs including etanercept withdrawn for 28 days prior to the first study medication dose (Day 1). These medications were not permitted for the duration of the study. Subjects were allowed to use stable, prescribed, low-dose corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin during the study.

Three (3) dose levels of abatacept were evaluated in this study: 0.5, 2, and 10 mg/kg. Abatacept was manufactured by Process D, and supplied in individual vials containing 200 mg of abatacept. Abatacept was administered by IV infusion over 1 hour on Days 1, 15, 29, and 57. A total of 90 subjects were administered abatacept. Of the 90 subjects, 8 subjects were enrolled in a site-specific PK substudy.

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. PK samples were obtained on day 1 (0, 0.5, 1, 2, 6, and 24 hours), day 8 (0 hours), day 15 (0, 0.5, and 1 hours), day 29 (0, 0.5, 1, 2, 6, and 24 hours), day 36, day 57 (0, 0.5, 1, 2, 6, and 24 hours), day 64, day 71, day 85, day 106, day 127, and day 169. PK parameters were derived from non-compartmental analysis.

**Results****Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters are presented below.

Treatment Dose [mg/kg]	Pharmacokinetic Parameters of Abatacept					
	Geometric Mean (%CV)				Mean (SD)	
	Cmax [µg/mL]		AUC(TAU) [µg-h/mL]		t <sub>1/2</sub> [Days]	
	Day 1	Day 57	Day 1	Day 57	Day 1	Day 57
0.5 (N=2)	13.7 (12)	7.5 (98)	1175 (15)	1168 (-) <sup>a</sup>	5 (0.8)	6.7 (4.1)
2.0 (N=3)	48.5 (20)	57.3 (29)	4453 (16)	5020 (37)	5.3 (1.2)	8 (2) <sup>b</sup>
10.0 (N=3)	269.6 (40)	263.9 (25)	22745 (27)	34732 (23)	5.4 (0.5)	10.6 (2.5)

a. N = 1 for AUC(TAU)

b. N = 2 for t<sub>1/2</sub>

Abatacept was administered by IV infusion over 1 hour on Days 1, 15, 29, and 57.

(Values in the table above are taken from Page 47 of the Clinical Pharmacology Summary.)

For doses of abatacept increasing in the ratio of 1.0: 4.0: 20.0, the geometric means for Day 1 Cmax increased in the ratio 1.0: 3.5: 19.7, Day 1 AUC(TAU) increased in the ratio 1.0: 3.8: 19.4, Day 57 Cmax increased in the ratio 1.0: 7.6: 35.1, and Day 57 AUC(TAU) increased in the ratio AUC(TAU) 1.0: 4.3: 29.7. These ratios suggest that over the range of doses studied, Cmax and

AUC(TAU) increase proportionally to dose on Day 1, but may increase more than proportionally to dose on Day 57. The number of subjects studied at each dose level was small; thus, the observations may not be generalizable to the RA population.

### **Conclusions**

- (1) Following a multiple dose regimen of IV administration (Days 1, 15, 29, and 57) in 8 RA subjects over a dose range of 0.5 to 10.0 mg/kg, abatacept exhibited nearly linear pharmacokinetics at Day 1, but greater than dose proportional pharmacokinetics at Day 57; the observations may not be generalizable to the RA population because of the small number of subjects studied at each dose level.

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**Study IM101100**

A Phase 2B, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Clinical Efficacy of Two Different Doses of BMS-188667 (Abatacept) Administered Intravenously to Subjects with Active Rheumatoid Arthritis While Receiving Methotrexate

**Methods**

This was a randomized, double-blind, placebo-controlled trial with parallel-dosing in subjects with active RA. Subjects were randomized 1:1:1 to receive IV infusions over 30 minutes of abatacept 10 mg/kg, abatacept 2 mg/kg, or placebo. Abatacept was administered IV to subjects on Days 1, 15, and 30, and every 30 days thereafter for a year. Subjects were maintained on a stable dose of MTX (10-30 mg/wk). Abatacept was manufactured by Process D, and supplied in individual vials containing 200 mg of abatacept.

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. Blood samples for PK analysis were collected prior to dosing on Days 1, 60, 90, and 180 from all 339 subjects. Additional blood samples for a more complete PK profile were collected during the dosing interval between Days 60 and 90 from 90 subjects participating in a site-specific PK substudy. For those subjects who participated in the PK substudy, blood samples were collected prior to dosing on Day 30, and for a PK profile beginning on Day 60, at 30 minutes, at 4 hours, and weekly thereafter until Day 90. PK parameters for subjects in the PK substudy were derived from non-compartmental analysis.

**Results****Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters from the PK substudy are presented in the tables below.

Treatment Dose [mg/kg]	Pharmacokinetic Parameters of Abatacept				
	Geometric Mean (%CV)		Mean (SD)		
	C <sub>max</sub> [µg/mL]	AUC(TAU) [µg-h/mL] *	t <sub>1/2</sub> [Days]	CL <sub>T</sub> [mL/h/kg]	V <sub>ss</sub> [L/kg]
2.0 (N=15)	54.9 (29)	9573.5 (30)	13.5 (5.9)	0.23 (0.13)	0.07 (0.04)
10.0 (N=14)	284.2 (23)	47624.2 (31)	13.1 (5.3)	0.22 (0.09)	0.07 (0.03)

Abatacept was administered by IV infusion over 30 minutes on Days 1, 15, 30, and every 30 days thereafter for a year. PK parameters were determined after the Day 60 dose.

\* TAU = 30 days

(Values in the table above are taken from Page 45 of the Clinical Pharmacology Summary.)

Treatment Dose [mg/kg]	Pharmacokinetic Parameters of Abatacept				
	Median (Range)				
	C <sub>max</sub> [µg/mL]	AUC(TAU) [µg-h/mL] *	t <sub>1/2</sub> [Days]	CL <sub>T</sub> [mL/h/kg]	V <sub>ss</sub> [L/kg]
2.0 (N=15)	59.6 (18.8-77.8)	11101.4 (3154.9-13927.5)	13.4 (8.0-31.5)	0.18 (0.14-0.63)	0.06 (0.03-0.19)
10.0 (N=14)	294.7 (170.6-397.9)	48882.1 (21279.1-79852.8)	12.3 (7.6-25.3)	0.20 (0.13-0.47)	0.06 (0.02-0.13)

Abatacept was administered by IV infusion over 30 minutes on Days 1, 15, 30, and every 30 days thereafter for a year. PK parameters were determined after the Day 60 dose.

\* TAU = 30 days

(Values in the table above are taken from Page 676 of the IM101100 Clinical Study Report.)

For nominal doses increasing in the ratio of 1: 5, the geometric means of C<sub>max</sub> increased in the ratio of 1: 5.2, while the geometric mean for AUC(TAU) increased in the ratio of 1: 5.0. Thus, the results suggest that both C<sub>max</sub> and AUC(TAU), where TAU = 30 days, increased in a dose proportional manner.

Values of t<sub>1/2</sub>, CL<sub>T</sub>, and V<sub>ss</sub> appeared to be independent of dose. The mean t<sub>1/2</sub> was approximately 13 days. The mean V<sub>ss</sub> of approximately 0.07 L/kg indicates that abatacept is confined primarily to the vascular system.

Summary statistics for C<sub>min</sub> assessed on Days 30, 60, 90 and 180 are presented below.

Summary Statistics Of C <sub>min</sub> Values [µg/mL] Assessed On Study Days 30, 60, 90 and 180			
Dose [mg/kg]	Study Day	Mean (SD)	Median (Range)
2.0	Day 30 Pre-Dose (N=21)	9.5 (3.4)	8.6 [ ]
	Day 60 Pre-Dose (N=94)	5.8 (11.5)	4.1
	Day 90 Pre-Dose (N=94)	4.4 (5.0)	3.2
	Day 180 Pre-Dose (N=82)	6.7 (16.8)	3.1
10.0	Day 30 Pre-Dose (N=20)	69.4 (98.6)	41.7
	Day 60 Pre-Dose (N=107)	28.7 (36.3)	22.4
	Day 90 Pre-Dose (N=99)	25.3 (36.9)	19.5
	Day 180 Pre-Dose (N=89)	22.0 (11.0)	20.2 [ ]

Abatacept was administered by IV infusion over 30 minutes on Days 1, 15, 30, and every 30 days thereafter for a year. (Values in the table above are taken from Page 677 of the IM101100 Clinical Study Report.)

Steady state conditions for abatacept appeared to be reached by the third monthly dose (Day 60). The mean C<sub>min</sub> steady-state values for all subjects receiving monthly intravenous doses of 2 and 10 mg/kg abatacept ranged between 4.4 to 6.7 µg/mL and 22.0 to 28.7 µg/mL, respectively. Serum concentrations appeared to be above steady-state trough concentrations during the first 2 months of treatment. Comparison of mean C<sub>min</sub> values at Days 60, 90, and 180 indicated that abatacept does not appear to accumulate following monthly dosing.

## **Conclusions**

- (1) Following a multiple dose regimen of IV administration (Days 1, 15, 30, and every 30 days thereafter for a year) over a dose range of 2.0 to 10.0 mg/kg, abatacept exhibited dose proportional increases in AUC(TAU) and C<sub>max</sub> after the Day 60 dose in RA subjects being co-administered MTX (10-30 mg/wk).
- (2) Mean t<sub>1/2</sub> value after the Day 60 dose was approximately 13 days and appeared to be independent of dose over the dose range studied (2.0 to 1.0 mg/kg).
- (3) V<sub>ss</sub> value after the Day 60 dose approximated plasma volume, indicating that abatacept (when given on a background of methotrexate) was confined primarily to the vascular system, and did not significantly distribute into extravascular spaces.
- (4) Following a multiple dose regimen of IV administration (Days 1, 15, 30, and every 30 days thereafter for a year) over a dose range of 2.0 to 10.0 mg/kg, abatacept appeared to reach steady state conditions by the third monthly dose (Day 60) in RA subjects being co-administered MTX (10-30 mg/wk).
- (5) Mean C<sub>min</sub> steady-state values for subjects receiving monthly intravenous doses of 2 and 10 mg/kg abatacept ranged between 4.4 to 6.7 µg/mL and 22.0 to 28.7 µg/mL, respectively.
- (6) Comparison of mean C<sub>min</sub> values at Days 60, 90, and 180 indicated that abatacept does not appear to accumulate following monthly dosing when given on a background of methotrexate.

**Study IM101101**

A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Safety and Clinical Efficacy of Intravenous Infusions of BMS-188667 (Abatacept, 2 mg/kg) Given Monthly in Combination With Subcutaneous Injections of Etanercept (25 mg) Given Twice Weekly to Subjects With Active Rheumatoid Arthritis

**Methods**

This was a randomized, double-blind, placebo-controlled trial with parallel-dosing in subjects with active RA. Subjects were randomized 2:1 to receive IV infusions over 30 minutes of abatacept 2 mg/kg, or placebo on a background of etanercept (25 mg SC twice weekly). Abatacept was administered IV to subjects on Days 1, 15, and 30, and every 30 days thereafter for a year. Abatacept was manufactured by Process D, and supplied in individual vials containing 200 mg of abatacept.

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. 85 subjects received 2 mg/kg of abatacept plus etanercept and 36 received placebo plus etanercept. Blood samples for PK analysis were collected prior to dosing on Days 1, 60, 90, and 180 from all 121 subjects. Additional blood samples for a more complete PK profile were collected during the dosing interval between Days 60 and 90 from 31 subjects participating in a site-specific PK substudy. For those subjects who participated in the PK substudy, blood samples were collected prior to dosing on Day 30, and for a PK profile beginning on Day 60, at 30 minutes (corresponding to the end of the infusion), at 4 hours after the start of the infusion, and weekly thereafter until Day 90. PK parameters for subjects in the PK substudy were derived from non-compartmental analysis. A total of 31 subjects participated in the PK substudy, but complete PK profiles between the dosing intervals from Day 60 to Day 90 were obtained from 6 subjects.

**Results****Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters are presented below.

Treatment Dose (mg/kg) *	Pharmacokinetic Parameters of Abatacept				
	Geometric Mean (%CV)		Mean (SD)		
	C <sub>max</sub> [µg/mL]	AUC <sub>(TAU)</sub> [µg-h/mL] *	t <sub>1/2</sub> [Days]	CL <sub>T</sub> [mL/h/kg]	V <sub>ss</sub> [L/kg]
2.0 (N = 6)	71.5 (21)	13708.4 (23)	13.2 (3.6)	0.15 (0.03)	0.05 (0.01)

Abatacept was administered by IV infusion over 30 minutes on Days 1, 15, 30, and every 30 days thereafter for a year. PK parameters were determined after Day 60 dose.

\* TAU = 30 days

(Values in the table above are taken from Page 46 of the Clinical Pharmacology Summary.)

The mean t<sub>1/2</sub> was approximately 13 days. The mean V<sub>ss</sub> of approximately 0.05 L/kg indicates that abatacept is confined primarily to the vascular system.



Summary statistics for C<sub>min</sub> assessed on Days 60, 90 and 180 are presented below.

Summary Statistics Of C <sub>min</sub> Values [µg/mL] Assessed On Study Days 30, 60, 90 and 180			
Dose [mg/kg]	Study Day	Mean (SD)	Median (Range)
2.0	Day 60 Pre-Dose (N=61)	4.80 (2.97)	4.07 $\bar{C}$ $\bar{J}$
	Day 90 Pre-Dose (N=59)	3.75 (2.86)	3.51 $\bar{C}$ $\bar{J}$
	Day 180 Pre-Dose (N=56)	3.34 (2.62)	2.96 $\bar{C}$ $\bar{J}$

Abatacept was administered by IV infusion over 30 minutes on Days 1, 15, 30, and every 30 days thereafter for a year. (Values in the table above are taken from Page 542 of the IM101101 Clinical Study Report.)

Steady state conditions for abatacept appeared to be reached by the third monthly dose (Day 60). The mean C<sub>min</sub> steady-state values for all subjects receiving monthly intravenous doses of 2 mg/kg abatacept ranged between 3.34 to 3.75 µg/mL.

Serum concentrations appeared to be above steady-state trough concentrations during the first 2 months of treatment. Comparison of mean C<sub>min</sub> values at Days 60, 90, and 180 indicated that abatacept does not appear to accumulate following monthly dosing.

### **Conclusions**

- (1) Following a multiple dose regimen of IV administration (Days 1, 15, 30, and every 30 days thereafter for a year) at a dose of 2.0 mg/kg, abatacept had a mean  $t_{1/2}$  value after the Day 60 dose of approximately 13 days in 6 RA subjects being co-administered etanercept (25 mg SC twice weekly).
- (2) V<sub>ss</sub> value after the Day 60 dose approximated plasma volume, indicating that abatacept (when given on a background of etanercept) was confined primarily to the vascular system, and did not significantly distribute into extravascular spaces.
- (3) Following a multiple dose regimen of IV administration (Days 1, 15, 30, and every 30 days thereafter for a year) at a dose range of 2.0 mg/kg, abatacept appeared to reach steady state conditions by the third monthly dose (Day 60) in 6 RA subjects being co-administered etanercept (25 mg SC twice weekly).
- (4) Mean C<sub>min</sub> steady-state values for subjects receiving monthly intravenous doses of 2 mg/kg abatacept ranged between 3.34 to 4.80 µg/mL in 6 RA subjects being co-administered etanercept (25 mg SC twice weekly).
- (5) Comparison of mean C<sub>min</sub> values at Days 60, 90, and 180 indicated that abatacept does not appear to accumulate following monthly dosing when given on a background of etanercept.

**Study IM101200**

A Phase 2, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Preliminary Efficacy, Pharmacokinetics and Immunogenicity of BMS-188667 Administered to Subjects with Relapsing-Remitting Multiple Sclerosis

**Methods**

This was a randomized, double-blind, placebo-controlled study where subjects identified with relapsing-remitting multiple sclerosis (MS) were randomized to receive either 2 mg/kg abatacept or 10 mg/kg abatacept or placebo. Infusions of abatacept were administered on Days 1, 15, and 29, and approximately every 4 weeks thereafter through Day 197 of the study. Abatacept for this study was manufactured by both Process D (supplied in individual vials containing 200 mg of abatacept), and by Process E (supplied in individual vials containing 250 mg of abatacept).

Abatacept levels in serum were assayed by an ELISA method. Lower limit of quantitation (LLQ) was 1 ng/mL. Blood specimens for determination of trough abatacept levels were collected just prior to dosing on Days 15, 29, 57, 85, 113, 141, 169, and 197, and approximately 28 days after final double-blind infusion. In addition, blood samples were collected for abatacept determination before dosing on Day 85 and for a pharmacokinetic profile beginning on Day 85 at 30 minutes (corresponding to the end of infusion), 2 hours and 6 hours after start of infusion, and weekly thereafter until Day 113. PK parameters for subjects in the PK substudy were derived from non-compartmental analysis.

**Results****Pharmacokinetic Results:**

Summary statistics for abatacept pharmacokinetic parameters are presented below.

Treatment Dose [mg/kg]	Pharmacokinetic Parameters of Abatacept				
	Geometric Mean (%CV)		Mean (SD)		
	Cmax [ $\mu\text{g/mL}$ ]	AUC(TAU) [ $\mu\text{g}\cdot\text{h/mL}$ ]	$t_{1/2}$ [Days]	CLT [ $\text{mL/h/kg}$ ]	Vss [ $\text{L/kg}$ ]
2.0 (N = 16)	52.6 (20)	13655.9 (20)	11.1 (3.0)	0.15 (0.03)	0.06 (0.01)
10.0 (N = 12)	233.1 (28)	69427.8 (22)	15.9 (6.7)	0.15 (0.04)	0.08 (0.03)

Abatacept was administered by IV infusion on Days 1, 15, and 29, and approximately every 4 weeks thereafter. (Values in the table above are taken from Page 48 of the Clinical Pharmacology Summary.)

The PK data indicated that both Cmax and AUC(TAU) values increased in a proportion approximately comparable to dose increment. For nominal doses increasing in the ratio of 1: 5, the geometric means of Cmax increased in the ratio of 1:4.4, and the AUC(TAU) increased in the ratio of 1: 5.1.

The mean  $t_{1/2}$ ,  $\text{CL}_T$  and Vss values appeared to be independent of dose. The mean Vss values were 0.06 and 0.08 L/kg for the 2 and 10 mg/kg groups, respectively, and indicates that abatacept stays primarily within the vascular system.

Summary statistics for Cmin assessed by day are presented below.

Summary Statistics Of Cmin Values [ $\mu\text{g/mL}$ ]				
Time [Day]	2.00 mg/kg dose		10.00 mg/kg dose	
	N	Mean(SD)	N	Mean(SD)
15.0	(N=43)	5.40 (1.69)	(N=23)	27.32 (7.58)
29.0	(N=43)	9.00 (6.07)	(N=21)	43.44 (13.73)
57.0	(N=39)	5.11 (1.90)	(N=23)	28.60 (9.39)
85.0	(N=24)	4.24 (2.32)	(N=17)	39.23 (48.13)
113.0	(N=32)	3.82 (1.65)	(N=14)	26.53 (9.71)
141.0	(N=27)	3.89 (1.72)	(N=14)	26.40 (7.95)
169.0	(N=27)	4.10 (1.75)	(N=13)	26.26 (9.05)
197.0	(N=24)	3.92 (1.91)	(N=12)	24.16 (11.22)
225.0	(N=27)	3.72 (2.16)	(N=13)	23.00 (7.56)
250.0	(N=10)	4.50 (2.76)	(N=4)	18.63 (6.43)

Abatacept was administered by IV infusion on Days 1, 15, and 29, and approximately every 4 weeks thereafter. (Values in the table above are taken from Pages 651 to 652 of the IM101200 Clinical Study Report.)

Steady-state conditions for abatacept in MS subjects appeared to be reached by the fifth infusion (i.e., Day 85). The mean Cmin steady-state values for all subjects receiving every 4 week intravenous doses of 2 and 10 mg/kg abatacept ranged between 3.72 to 4.50  $\mu\text{g/mL}$  and 18.63 to 39.23  $\mu\text{g/mL}$ , respectively.

Serum concentrations appeared to be above trough steady-state concentrations during the first 2 months of treatment. Comparison of mean Cmin values at Days 57, 85, 113, 141, 169, 197, 225, and 250 suggested that abatacept does not accumulate following every 4 week dosing.

## **Conclusions**

- (1) Following a multiple dose regimen of IV administration (Days 1, 15, and 29, and approximately every 4 weeks thereafter) over a dose range of 2.0 to 10.0 mg/kg, abatacept exhibited dose proportional increases in AUC(TAU) and Cmax after the Day 85 dose in relapsing-remitting MS subjects.
- (2)  $t_{1/2}$ ,  $CL_T$ , and  $V_{SS}$  values appeared to be dose independent over the dose range studied (2.0 to 10.0 mg/kg) in relapsing-remitting MS subjects.
- (3)  $V_{ss}$  value after the Day 85 dose approximated plasma volume, indicating that abatacept was confined primarily to the vascular system, and did not significantly distribute into extravascular spaces, in relapsing-remitting MS subjects.
- (4) Following a multiple dose regimen of IV administration (Days 1, 15, and 29, and approximately every 4 weeks thereafter), steady-state conditions for abatacept at doses of 2 and 10 mg/kg were reached by the fifth dose (Day 85) in relapsing-remitting MS subjects.
- (5) Mean Cmin steady-state values for all subjects receiving every 4 week intravenous doses of 2 and 10 mg/kg abatacept ranged between 3.72 to 4.50  $\mu\text{g/mL}$  and 18.63 to 39.23  $\mu\text{g/mL}$ , respectively, in relapsing-remitting MS subjects.
- (6) Comparison of mean Cmin values at Days 57, 85, 113, 141, 169, 197, 225, and 250 indicated that abatacept does not appear to accumulate following every 4 week dosing, in relapsing-remitting MS subjects.

## COMPARISONS AND ANALYSES ACROSS STUDIES

### Population PK Analysis

#### A Population Pharmacokinetics Analysis for Abatacept

The objectives of this population pharmacokinetic (POPPK) analysis were to develop and validate a 2-compartment POPPK model for abatacept, to characterize abatacept PK in the target rheumatoid arthritis (RA) subject population, and to identify and quantify covariates which may affect the PK of abatacept.

### Methods

#### Datasets:

The results of three Phase 2 RA studies (IM103002, IM101100, and IM101101) and three Phase 3 RA studies (IM101102, IM101029, and IM101031) were used in the population PK analysis. The study design and methods for each of the three Phase 2 RA studies were described earlier. A summary of the population PK sampling and analysis plan for the Phase 3 Studies is presented in [Appendix 1](#).

The model building and internal validation data sets were created from the Phase II data. Twenty percent (20%) of the Phase II data were set aside as the internal model validation dataset, while the remaining eighty percent (80%) was used as the model-building dataset. The generation of the model building and internal validation datasets was based on random data splitting on a per subject basis, with the constraint in the splitting method that all subjects ( $n = 8$ ) from the IM103002 study were included in the model-building dataset due to its data rich nature. There were 190 subjects included in the model-building dataset and 48 subjects included in the internal validation dataset.

The external validation dataset consisted of a randomly selected subset of subjects with PK samples collected during the data-rich Day 85 to Day 113 dosing period from the three Phase 3 studies. Fifty subjects from each of the three Phase 3 studies were randomly selected for a total of 150 subjects. (see [Appendix 1](#))

#### Model:

A hierarchical POPPK model was built with use of the NONMEM computer program (version 5, level 1.1). A base model was first developed that consisted of a structural PK model with PK parameters such as clearance and a pharmaco-statistical model describing inter-individual variability on PK parameters and intra-individual variability. Covariate sub-models that quantitatively describe covariate effects on model PK parameters were evaluated and added sequentially to the base model and compared with the base model using the likelihood ratio test. Model building followed standard procedures and utilized a forward addition/backwards elimination method at  $p < 0.001$ . Other considerations for covariate acceptance included clinical or physiological relevance, reduction in inter-individual variability, and improvement in goodness-of-fit plots (such as population prediction versus observed concentrations, and weighted residual versus population prediction plots). Covariates with an average difference of greater than 20%

were identified for further analysis. The following covariates were evaluated: body weight, age, gender, concomitant medication, disease state and duration of disease at baseline, creatinine clearance, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Model qualification was conducted with internal and external validation databases. Both concentration predictive performance and PK parameter predictive performance checks were employed for both the internal and external validation datasets.

## Results

### Model:

A 2-compartment POPPK model with zero-order infusion and 1st-order elimination was used. The model had a constant coefficient of variation residual error model for both sparse and dense data, and a separate additive term for the sparse data. (Dense data was defined as any subject with greater than or equal to 4 ( $\geq 4$ ) pharmacokinetic samples drawn over a dosing interval; sparse data was defined as any subject with less than 4 samples over a dosing interval.) The model included terms for inter-individual variability on clearance, and also the central and peripheral volumes of distribution. There were terms describing the correlation between clearance and the central volume of distribution, and between the central and peripheral volumes of distribution.

The equations for the final population PK model parameters are given in the equation below.

$$CL_{TV} = CL_0 + CL_1 \cdot \frac{WT}{WT_{REF}}$$

$$CL = CL_{TV} \cdot \exp(\eta_{CL})$$

$$V1 = V1_{TV} \cdot \exp(\eta_{V1})$$

$$Q = Q_{TV}$$

$$V2 = V2_{TV} \cdot \exp(\eta_{V2})$$

where  $CL_0$ ,  $CL_1$ ,  $V1$ ,  $V2$  and  $Q$  are model parameters, and the TV subscript denotes the population average value of a PK parameter, the  $\eta$ 's denote the interindividual variability of the parameter,  $WT$  denotes the body weight of an individual subject, and  $WT_{REF}$  is the reference bodyweight of 78.9 kg.

(The equation above is taken from Page 20 of the Population PK Clinical Study Report.)

The final parameter estimates and their associated standard errors are provided below.

Final Population PK Model Parameter Estimates - Combined (Phase II and III) Dataset		
Parameter [Units]	Population Average [SE%] <sup>a</sup>	IIVb [SE%]
$CL_0$ [L/day]	0.333 (9.85)	29.3 <sup>c</sup> (12.4)
$CL_1$ [L/day]	0.210 (16.1)	
$V1$ [L]	3.22 (2.45)	24.2 (16.9)
$Q$ [L/day]	0.525 (11.4)	----
$V2$ [L]	4.68 (6.1)	35.1 (34.4)

a. SE as % of percentage of population average

b. IIV is Inter-subject Variability (% Population Average), with SE is expressed as a % of IIV variance.

c. % IIV of  $CL$  is calculated with respect to  $CL_0 + CL_1$

(Values in the table above are taken from Page 21 of the Population PK Clinical Study Report.)

Final Population PK Model Proportional and Additive Residual Error - Combined (Phase II and III) Dataset	
	Residual Error [SE%]
Proportional Residual Error [%CV]	24.9 (9.50)
Additive Residual Error [ $\mu\text{g/mL}$ ]	1.32 (59.5)

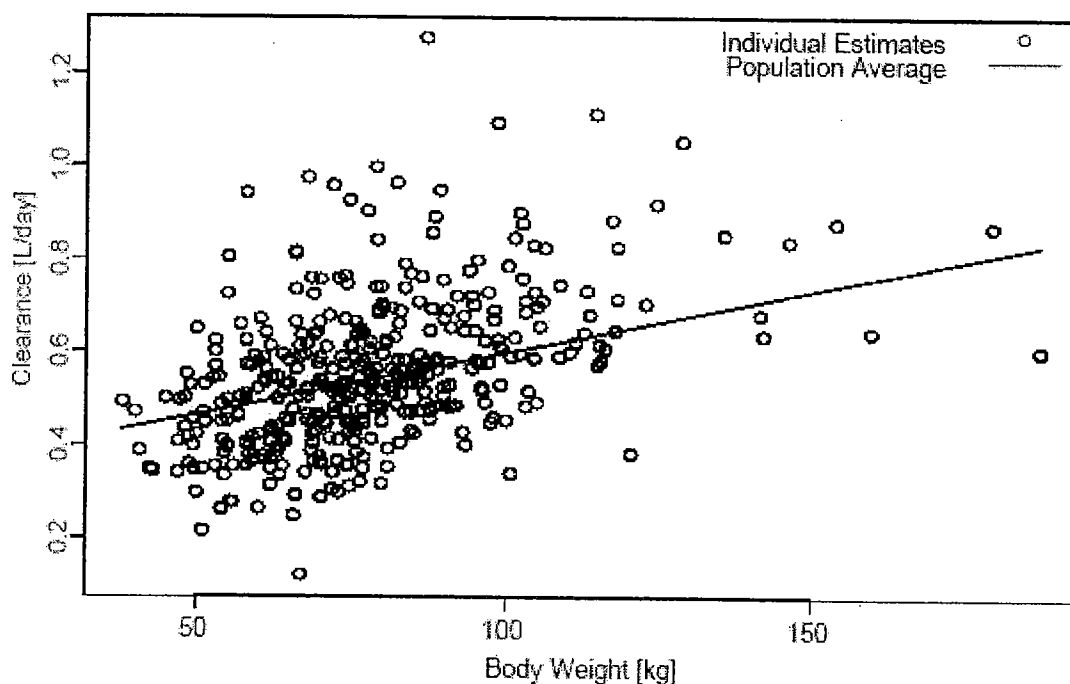
(Values in the table above are taken from Page 21 of the Population PK Clinical Study Report.)

### Effect of Body Weight:

The effect of body weight on clearance was the only statistically significant covariate identified during this analysis. Adding normalized weight as a linear function to clearance reduced the objective function by 38.7 points and reduced the inter-individual variability on clearance from 31% in the base model to 28% in the final model. Residual variability was not altered by the addition of this covariate sub-model, nor were the parameter standard errors changed.

The effect of body weight on clearance determined in the POPPK analysis is shown in the figure below.

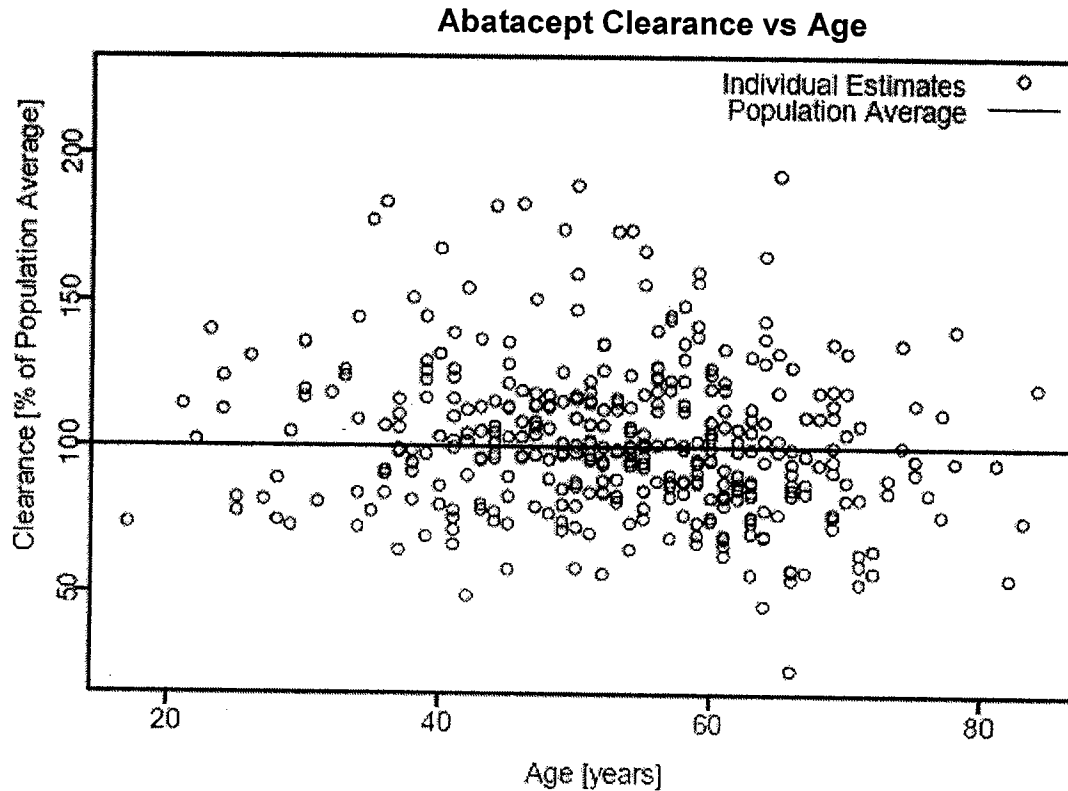
**Abatacept Clearance vs Body Weight**



The line showing the population average value of clearance for subjects with a given body weight represents the population geometric mean of the lognormal distribution of clearance, as a function of weight. (The figure above is taken from Page 68 of the Clinical Pharmacology Summary.)

Effect of Age:

The distributions of individual estimates of clearance with respect to age are shown in the figure below.



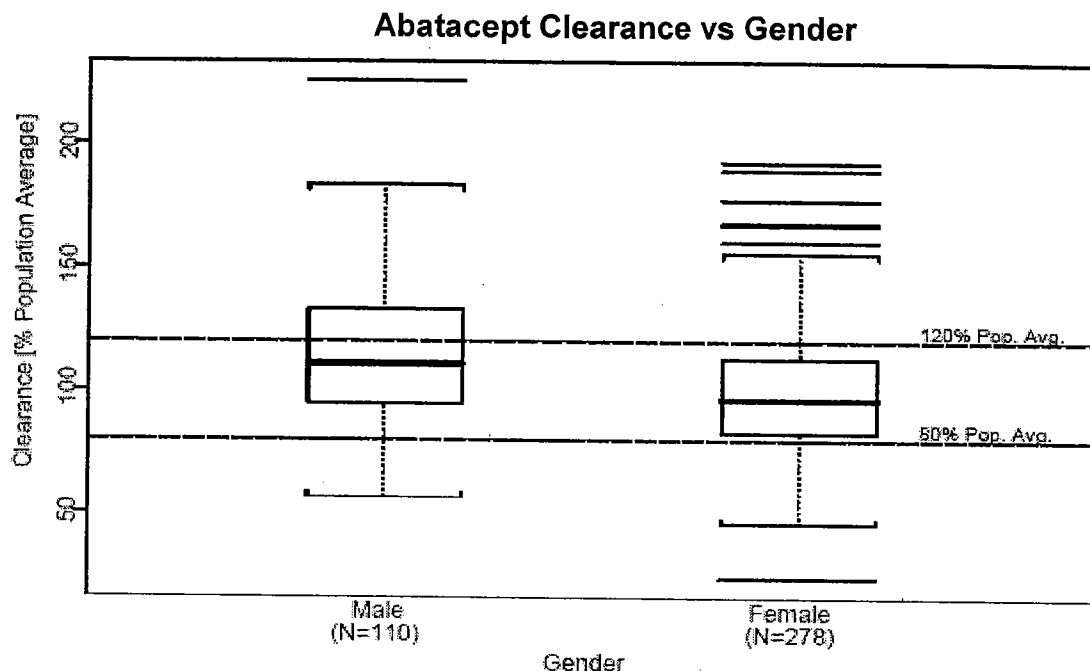
(The figure above is taken from Page 73 of the Clinical Pharmacology Summary.)

The scatter pattern of the individual clearance vs age in the figure above suggests that age does not have a significant effect on abatacept clearance.

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Effect of Gender:

The distributions of individual estimates of clearance with respect to gender are shown in the box-and-whisker plot below.



The lower and upper end of the boxes represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles. The bold line represents the median. Horizontal dotted lines at 80% and 120% population average put differences between the groups in perspective. (The figure above is taken from Page 73 of the Clinical Pharmacology Summary.)

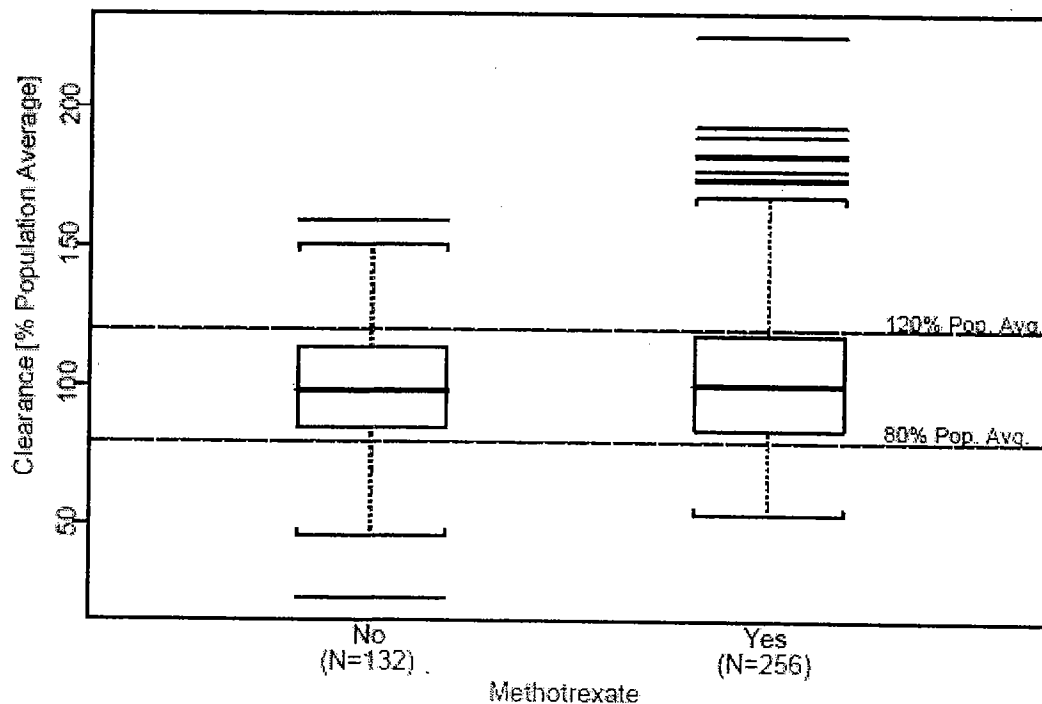
The box-and-whisker plot suggests that females have a slightly lower clearance than male subjects, even after accounting for the effect of body weight. The ratio of the geometric mean of clearance of females relative to males was 0.86, suggesting that gender differences do not appear to be clinically relevant. This ratio of the geometric mean clearances is expected to be relatively robust, given the large number of subjects in each gender group (females, N = 278 and males, N = 110) available for the analysis.

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Effect of Concomitant Medications:

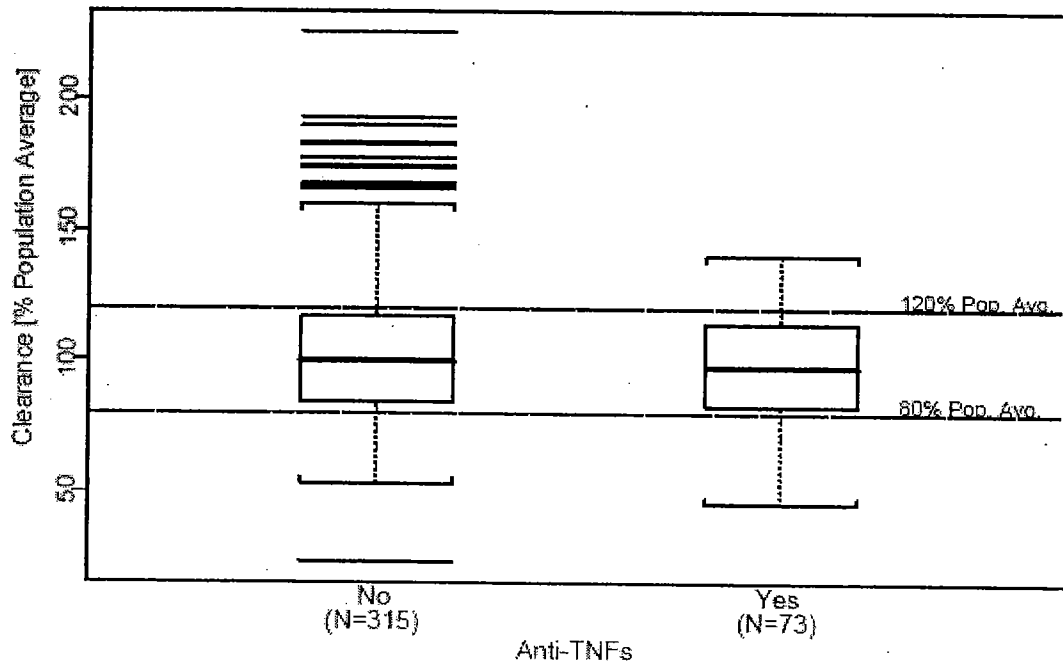
Several commonly co-administered medications (methotrexate, corticosteroids, NSAIDs, and anti-TNF blocking agents) were investigated. The ratios of the geometric means of clearance of subjects on a given co-medication relative to all the other subjects were 1.04 for MTX, 0.99 for NSAIDs, 1.09 for corticosteroids, and 0.97 for the anti-TNF blocking agents, well below the 20% threshold, and as such, no additional analysis were performed. The distribution of individual clearance estimates as a function of co-administered drug is shown as box-and-whisker plots in the figures below.

**Abatacept Clearance With Respect to MTX Co-Administration**

(The figure above is taken from Page 70 of the Clinical Pharmacology Summary.)

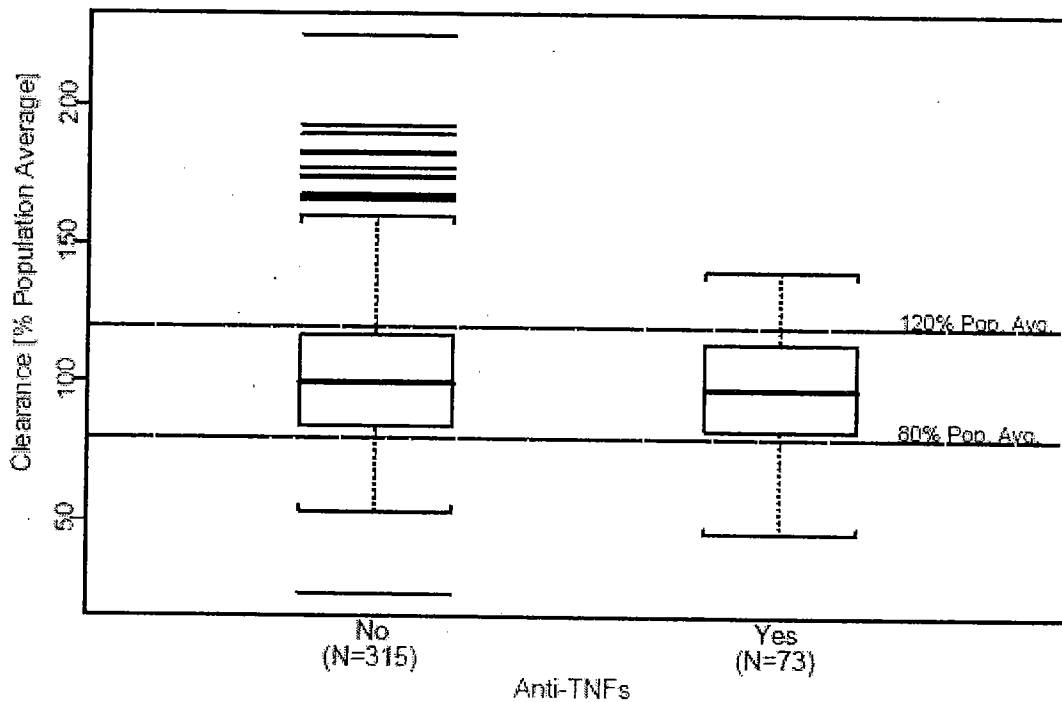
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### Abatacept Clearance With Respect to Anti-TNF Co-Administration



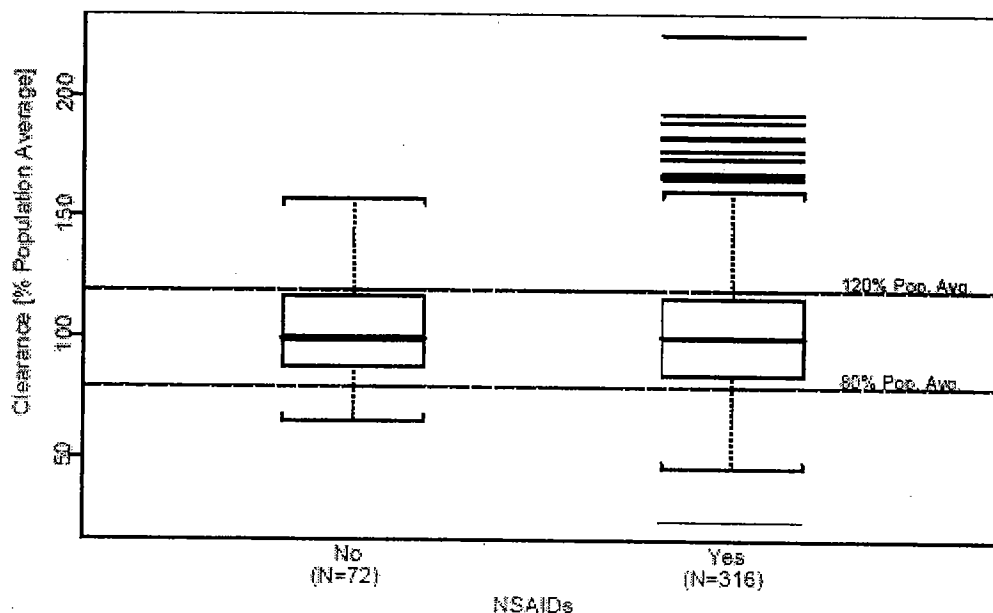
(The figure above is taken from Page 71 of the Clinical Pharmacology Summary.)

### Abatacept Clearance With Respect to Corticosteroid Co-Administration



(The figure above is taken from Page 71 of the Clinical Pharmacology Summary.)

### Abatacept Clearance With Respect to NSAID Co-Administration



(The figure above is taken from Page 72 of the Clinical Pharmacology Summary.)

These results indicate that these commonly co-administered drugs had very little impact on the PK of abatacept. No dose adjustment of abatacept would therefore be needed when abatacept is co-administered with MTX, corticosteroids, NSAIDs, and the anti-TNF blocking agents.

#### Effect of Disease State and Duration of Disease at Baseline:

Effects of disease state measures at baseline on abatacept PK parameters were evaluated. Disease state at baseline was assessed using tender joint counts and swollen joint counts. Duration of disease at baseline was indicated by years. The results indicated no clear trend to suggest that disease states and the duration of disease contributed to changes in abatacept PK parameters.

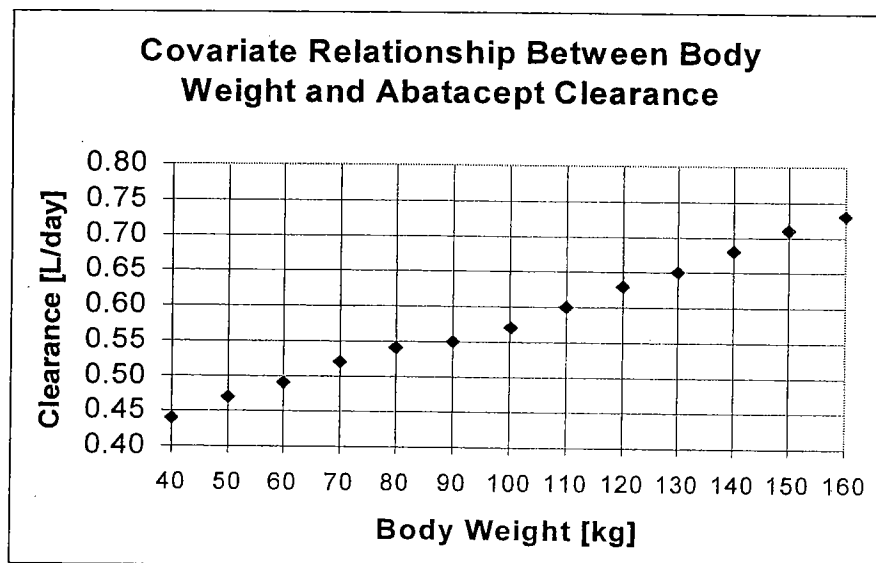
#### Effect of Renal and Hepatic Status:

The relationship between abatacept clearance and measures of serum creatinine and the liver enzymes, ALT and AST, were evaluated in the development of the POPPK model. The results indicated that these covariates had no effect on the clearance of abatacept or on the volume of distribution of the central compartment. It should be noted that the majority of subjects had adequate hepatic and renal function since these were clinical study inclusion criteria.

#### Comparison of Dose-Adjusted Steady State AUC:

For the Phase III studies, a fixed dose regimen (500 mg for subjects weighing < 60 kg, 750 mg for subjects weighing between 60 and 100 kg, and 1000 mg for subjects weighing > 100 kg) was selected, representing a dose approximating 10 mg/kg  $\pm$  25% for each weight range.

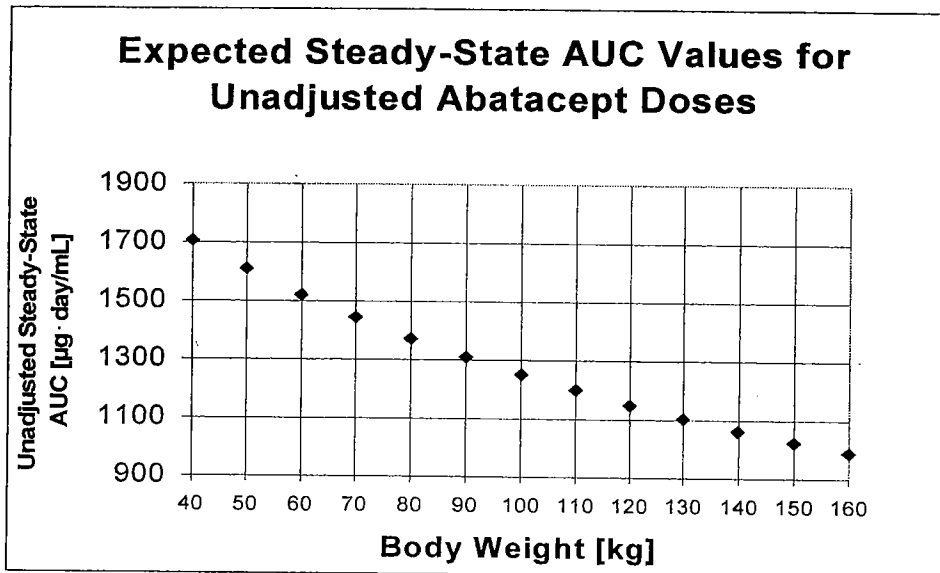
The results of the POPPK analysis indicated that abatacept clearance increased with body weight. The median body weight of subjects in the Phase II and III trials (for whom pharmacokinetic data were available) ranged from 38.1 to 159.5 kg, with a mean weight of 77.0 kg. The figure below provides an evaluation of the effect of body weight on abatacept clearance over the range of subject weights found in the target RA population. Clearance was calculated using the final parameters obtained from the final pharmacokinetic model.



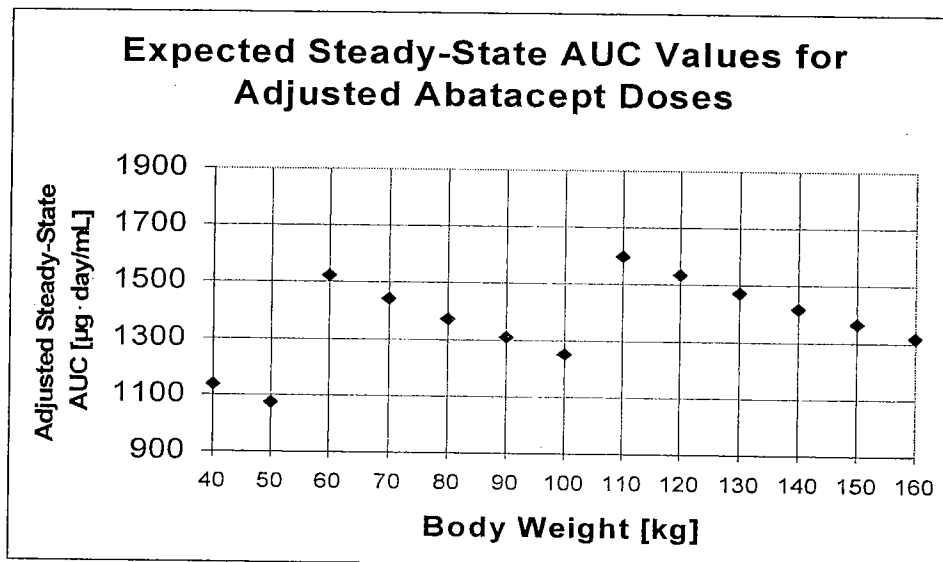
(Values plotted in the figure above were taken from Page 77 of the Clinical Pharmacology Summary.)

From the figure above, subjects weighing 40 kg and 160 kg are expected to have differences in clearances of approximately 19% lower and 35% higher, respectively, relative to the subject weighing 80 kg. Therefore, the effect of weight is substantial and clinically relevant, making a weight-based dose regimen important to control the inter-individual variability of exposure to abatacept. The impact of the recommended body weight-based dose adjustment on the AUC of abatacept within a dosing interval at steady state (or equivalently the AUC(INF)) was therefore evaluated.

The figures below compare the expected steady-state AUC values for unadjusted and adjusted abatacept doses. The steady-state AUC was calculated using the relationship  $AUC = \text{Dose} / CL$ , and clearance was calculated using the parameters obtained from the final model. As the kinetics of abatacept are linear, the steady state AUC within a dosing interval can be equated with AUC(INF). In the unadjusted calculations, a uniform dose of 750 mg was used; in the adjusted calculations, the proposed dose regimen was used.



(Values plotted in the figure above were taken from Page 78 of the Clinical Pharmacology Summary.)

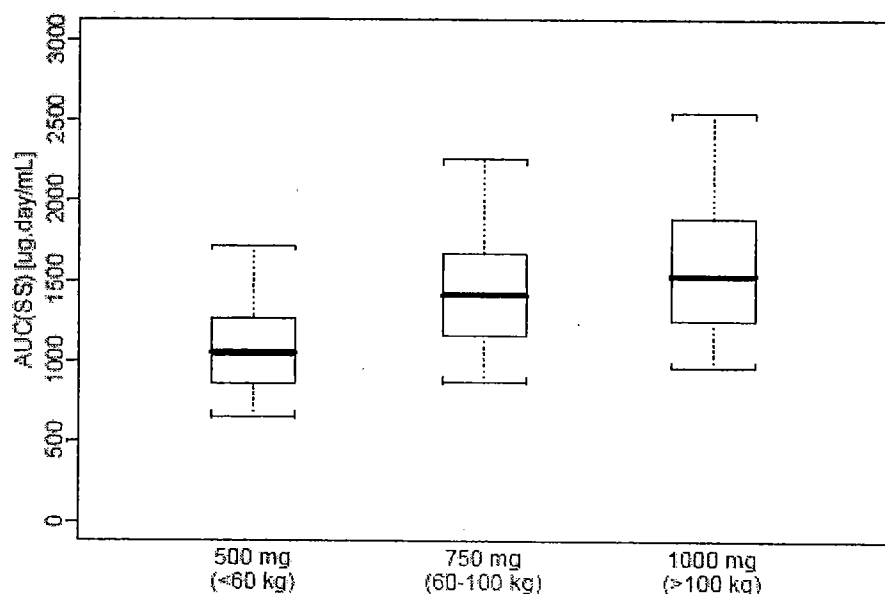


(Values plotted in the figure above were taken from Page 78 of the Clinical Pharmacology Summary.)

The necessity for dose adjustment is illustrated by the large range of average exposures with unadjusted dosing (988 to 1707  $\mu\text{g} \cdot \text{day/mL}$ ), relative to the range of average exposures with adjusted dosing (1073 to 1598  $\mu\text{g} \cdot \text{day/mL}$ ).

The distribution of the steady-state AUCs for the target population subjects were also simulated based on the observed body weight distribution and the proposed weight adjusted dose regimen. The distribution of the simulated steady-state AUCs in each of the recommended dose groups ( $N = 1000/\text{dose group}$ ) is shown in the figure below.

### Distribution of Simulated Steady-State AUC



Legend: Median = Bold line; Boxes = 25th/75th percentile; Whiskers = 5th/95th percentile  
 (The figure above is taken from Page 79 of the Clinical Pharmacology Summary.)

The results of the simulations showed that approximately 26% of the AUCs in the 500-mg dose group were less than the lower 5<sup>th</sup> percentile of AUCs in the 750 mg dose group, and approximately 10% of the AUCs in the 1000 mg dose group were higher than the 95<sup>th</sup> percentile of AUCs in the 750 mg dose group.

### Conclusions

- (1) The effect of body weight on clearance was the only statistically significant covariate identified; the higher clearance of abatacept with increasing weight supported a weight-adjusted dosing strategy.
- (2) With regard to gender, female subjects had a slightly lower clearance than male subjects; the ratio of the geometric mean of clearance of females relative to males was 86%, suggesting that gender differences do not appear to be clinically relevant.
- (3) No trends were noted for age, serum creatinine, ALT, AST, or disease status.
- (4) No trends were noted for co-administration of methotrexate, corticosteroids, NSAIDs, or anti-TNF blocking agents.
- (5) Comparison of the simulated dose-adjusted steady-state AUC values supported the Phase 3 fixed dose regimen in providing comparable exposure across the dose groups.

## **Drug Interactions**

### **Effect of Methotrexate and Etanercept**

An assessment of the impact of methotrexate (MTX) and etanercept (ETAN) on the PK of abatacept was obtained by comparing the non-compartmental PK results obtained from IM101100 (subjects were treated with abatacept in combination with methotrexate), IM101101 (subjects were treated with abatacept in combination with etanercept), and with data from IM101200 (subjects were treated with neither methotrexate nor etanercept). This comparison is summarized in the table below.

Non-Compartmental PK Parameters of Abatacept Across Studies						
Study	Dose	PK Parameter				
		C <sub>max</sub> [µg/mL]	AUC(TAU) [µg-h/mL]	t <sub>1/2</sub> [Days]	CL <sub>T</sub> [mL/h/kg]	V <sub>ss</sub> [L/kg]
		GM (% CV)	GM (% CV)	Mean (SD)	Mean (SD)	Mean (SD)
IM101100 (with MTX)	2 mg/kg (N = 15)	54.9 (29)	9573.5 (30)	13.5 (5.9)	0.23 (0.13)	0.07 (0.04)
	10 mg/kg (N = 14)	284.2 (23)	47624.2 (31)	13.1 (5.3)	0.22 (0.09)	0.07 (0.03)
IM101101 (with ETAN)	2 mg/kg (N = 6)	71.5 (21)	13708.4 (23)	13.2 (3.6)	0.15 (0.03)	0.05 (0.01)
IM101200 (without MTX/ETAN)	2 mg/kg (N = 16)	52.6 (20)	13655.9 (20)	11.1 (3.0)	0.15 (0.03)	0.06 (0.01)
	10 mg/kg (N = 12)	233.1 (28)	69427.8 (22)	15.9 (6.7)	0.15 (0.04)	0.08 (0.03)

GM: Geometric Mean

(Values in the table above were taken from Page 62 of the Clinical Pharmacology Summary)

This comparison is not optimal and is made across disease states; however, the results in the table above indicate that similar abatacept PK parameter values were obtained, suggesting that there was no clinically relevant change in the PK of abatacept with concomitant administration of methotrexate or etanercept.

## **Conclusions**

- (1) Comparison of the non-compartmental PK results obtained from IM101100 (co-administration of methotrexate), IM101101 (co-administration of etanercept), and from IM101200 (co-administration of neither methotrexate nor etanercept) suggested that there was no clinically relevant change in the PK of abatacept with concomitant administration of methotrexate or etanercept.

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## CONCLUSIONS

- (1) Abatacept demonstrated approximately dose proportional PK with systemic exposures to abatacept increasing as a function of dose regardless of the route of administration, IV or SC.
- (2) The mean  $t_{1/2}$  values of abatacept following IV administration in psoriasis subjects over the dose range of 0.5 to 50 mg/kg ranged between 10 and 19 days, and appeared to be independent of dose; mean  $t_{1/2}$  values of abatacept following SC administration in psoriasis subjects over the dose range of 1 to 8 mg/kg ranged between 9 and 13 days, and appeared to be independent of dose.
- (3) The mean  $t_{1/2}$  values of abatacept at a dose of 10 mg/kg in RA, MS, and healthy subjects following IV administration was approximately 13, 16, and 17 days, respectively.
- (4) Across multiple studies, the mean  $CL_T$  values after IV administration ranged between 0.16 and 0.23 mL/h/kg.
- (5) Across multiple studies, the mean volume of distribution at steady-state ( $V_{ss}$ ) values ranged between 0.07 and 0.10 L/kg. The small  $V_{ss}$  value indicates that abatacept is confined primarily to the vascular system.
- (6) Steady-state Conditions:
  - (a) With the proposed regimen (doses administered at Days 1, 15, 30, and every 30 days thereafter), steady-state conditions were achieved at approximately the third monthly dose (Day 60).
  - (b) Based on  $C_{min}$  serum concentrations taken prior to the administration of the third, fourth, and seventh monthly abatacept doses, accumulation was minimal.
  - (c) The mean  $C_{min}$  steady-state values for RA subjects receiving monthly IV doses of 10 mg/kg abatacept ranged between 22 and 29  $\mu$ g/mL.
- (7) Process Changes: Single dose pharmacokinetics of Process D and Process E abatacept were comparable based on  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{\infty}$  after an IV infusion of 10 mg/kg in healthy subjects.
- (8) Drug Interactions: Comparison of the non-compartmental PK results obtained after co-administration of methotrexate, co-administration of etanercept, and co-administration of neither methotrexate nor etanercept suggested that there was no clinically relevant change in the PK of abatacept with concomitant administration of methotrexate or etanercept.
- (9) Population PK Analysis:
  - (a) In a population PK analysis of 193 patients, the effect of body weight on clearance was the only statistically significant covariate identified; the higher clearance of abatacept with increasing weight supported the proposed weight-adjusted dosing strategy.
  - (b) With regard to gender, female subjects had a slightly lower clearance than male subjects; the ratio of the geometric mean of clearance of females relative to males was 86%, suggesting that gender differences do not appear to be clinically relevant.
  - (c) No trends were noted for age, serum creatinine, ALT, AST, or disease status.
  - (d) No trends were noted for co-administration of methotrexate, corticosteroids, NSAIDs, or anti-TNF blocking agents.
  - (e) Comparison of the simulated dose-adjusted steady-state AUC values supported the Phase 3 fixed dose regimen in providing comparable exposure across the dose groups.



## RECOMMENDATIONS

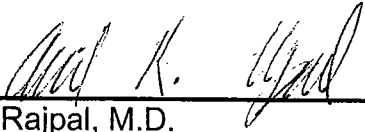
Revisions are recommended to the CLINICAL PHARMACOLOGY: Pharmacokinetics section as shown below.

### Pharmacokinetics

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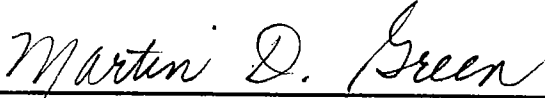
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June 17, 2005

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Anil K. Rajpal, M.D.  
Clinical Pharmacology Reviewer



June 19, 2005

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Martin D. Green, Ph.D.  
Associate Director for Pharmacology and Toxicology, ODE VI

**APPENDIX 1****Summary of Population PK Sampling and Analysis Plan from Phase 3 Studies**Study IM101102:

A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Abatacept (BMS-188667) in Combination Therapy With Methotrexate Versus Methotrexate Alone in Subjects With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate.

Infusion doses of abatacept were administered on Days 1, 15, and 29, and every 28 days thereafter for a year. Trough concentrations were obtained prior to dosing on all dosing days. A sparse sampling schedule was instituted between dosing Days 85 and 113. On Days 85 and 113, samples were collected before dosing and at the end of infusion. A single sample was also collected at any time between Days 92 to 98, and again at any time between Days 101 to 107. Based on the revised POPPK plan, analytical data from these 50 randomly selected subjects with dense PK sampling from this study were combined with data from IM101029 and IM101031 to provide an integrated Phase 3 PK database for the population PK analysis.

Study IM101029:

A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Abatacept (BMS-188667) Versus Placebo in Subjects with Active Rheumatoid Arthritis on Background DMARDs Who Have Failed Anti-TNF Therapy.

Infusion doses of abatacept were administered on Days 1, 15, and 29, and every 28 days thereafter for 6 months. For PK evaluation, samples were obtained from subjects prior to the administration of the IV infusion on all dosing days. Between Days 85 and 113, a sparse sampling schedule was instituted. Samples were collected pre-dose and at the end of the infusion on Days 85 and 113, and single samples were also obtained at any time between Days 92 to 98 and again at any time between Days 101 to 107. The analytical data from these 50 randomly selected subjects with dense PK sampling from this study were combined with data from IM101102 and IM101031 to provide an integrated Phase 3 PK database for the POPPK analysis.

Study IM101031:

A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Use Study to Evaluate the Safety and Tolerability of Abatacept (BMS-188667) Administered Intravenously to Subjects with Active Rheumatoid Arthritis (RA) With or Without Medical Co-Morbidities Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs) and/or Biologics Approved for RA.

Infusion doses of abatacept were administered on Days 1, 15, and 29, and every 28 days thereafter for a year. Trough samples were obtained prior to the IV infusions on Days 1, 29, 85, 169, and 281. An end of infusion (C<sub>max</sub>) sample was also obtained on dosing Day 85. The analytical data from the 50 randomly selected subjects from this study were combined with data from IM101029 and IM101102 to provide an integrated Phase 3 PK database for the POPPK analysis.

Comments on BLA125118 Orencia (abatacept)  
From A. Jacobs, Assoc Dir Pharm/tox  
12/23/05

*Wynne Jacobs* 12/23/05

Labeling:

Carc section:

The findings in the mammary gland are equivocal at best. The statistical analysis pooled the saline and vehicle controls, which is generally considered inappropriate. The incidence of mammary neoplasms in the vehicle controls is higher than ever seen in historicals at the test lab. The incidence in the mid dose is not statistically higher than that in the vehicle controls and it is doubtful that the incidence in the high dose is statistically significantly higher than that in the vehicle controls by the criteria that the CDER executive uses. Furthermore, mammary neoplasms have not been seen in CD-1 mice with other immunosuppressants, although lymphomas are nearly always seen. However, the labeling could be left alone at this time.

Line 251 vs line 254: it is confusing that in line 251 it says that 200 mg/kg in rats is 11-fold the human exposure (fertility study) and in line 254 that 200 mg/kg in rats is 29-fold the human exposure (teratogenicity study). This could be clarified by adding that the 200 mg/kg in line 251 was administered every 3 days and the 200 mg/kg in line 254 was administered every day.

Pregnancy category:

Although the Ghantous pharm/tox review recommends category I think the data and the low multiple of human exposure, coupled with the fact that the biologic crosses the placenta, warrant a category C, as stated in the draft labeling.

The wording of the labeling regarding effects on immune function for the F1 generation is somewhat inconsistent with the Ghantous review which says the effect on T-cell dependent antibody response was drug-related in female pups-(plural). (pp. 5 and 67) and with the O'Connor review (p. 4), which also says pups. Neither review described the immune effects as "limited". The wording in the proposed labeling lines 258-260 is confusing. I suggest the following rewording based on the Pharm/tox reviews:

Line 258: AUC, (New--- *alterations of immune function consisted of a 9-fold increase in the T-cell antibody response in female pups and inflammation of the thyroid in one female pup.*)

There are no pharm/tox approval issues.