

Clinical Protocol IM101034:

A Phase I, Multi-Center, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, Immunogenicity and Preliminary Efficacy of Escalating Doses of BMS-188667 (CTLA4Ig) Given as Single and Multiple Intravenous Infusion in Combination with DMARDs to Subjects with Rheumatoid Arthritis

Interim Report

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EXECUTIVE SUMMARY

Date of Report: 3-FEB-2006

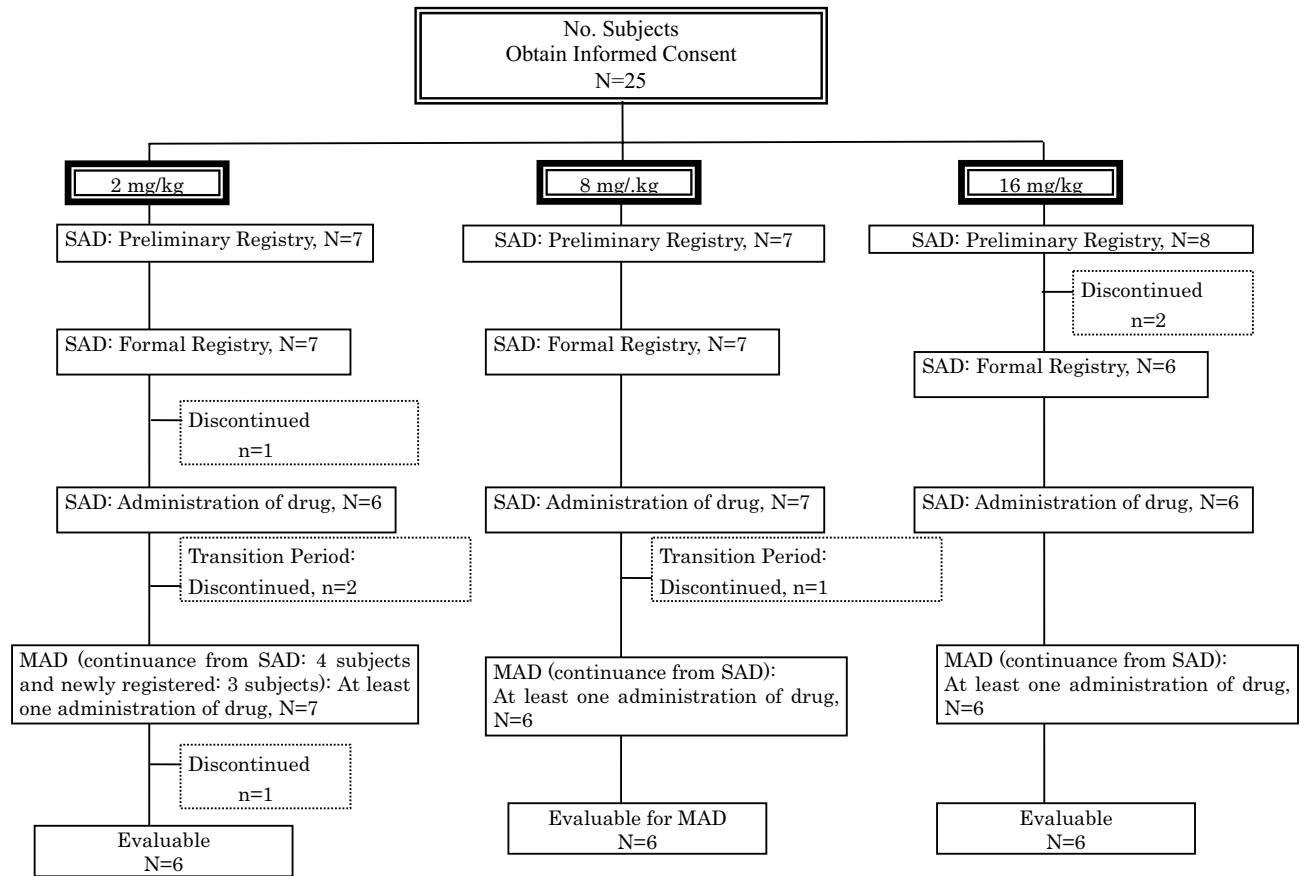
Title of Study: Protocol IM101034: A Phase I, Multi-Center, Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, Immunogenicity and Preliminary Efficacy of Escalating Doses of BMS-188667 (CTLA4Ig) Given as Single and Multiple Intravenous Infusion in Combination with DMARDs to Subjects with Rheumatoid Arthritis	
Investigators/Study Centers and Countries: 9 Study Center in Japan	
Publication (reference): None	
Study Period (First Patient First Visit to Last Patient Last Visit): 10-Feb-2002 to 29-DEC-2005	Study Phase: I
Research Hypothesis: BMS-188667 is safe and well tolerated in Japanese subjects with rheumatoid arthritis.	
Primary Objective: To assess the safety and tolerability of BMS-188667 (2, 8, and 16 mg/kg) in subjects with rheumatoid arthritis when this drug is administered as single and multiple doses by intravenous infusion.	
Secondary Objectives: <ul style="list-style-type: none"> • To assess the pharmacokinetics of BMS-188667 (2, 8, and 16 mg/kg) in subjects with rheumatoid arthritis when this drug is administered as single and multiple doses by intravenous infusion. • To assess the immunogenicity of BMS-188667 (2, 8, and 16 mg/kg) in subjects with rheumatoid arthritis when this drug is administered as single and multiple doses by intravenous infusion. • To assess the preliminary efficacy of BMS-188667 (2, 8, and 16 mg/kg) in subjects with rheumatoid arthritis when this drug is administered as multiple doses by intravenous infusion. • To assess the preliminary pharmacodynamics of BMS-188667 (2, 8, and 16 mg/kg) in subjects with rheumatoid arthritis when this drug is administered as multiple doses by intravenous infusion. 	
Study Design: Dose-escalation, single and multiple doses, central registration, multicenter cooperative open-label study; This study is comprised of a lead-in period, a single dose phase, a transition period and a multiple dose phase. In the lead-in period, preliminary registration will be conducted after obtaining written consent from the subjects. After completion of preliminary registration of 7 subjects at each dose, the target number of subjects, formal registration will be initiated. After the completion of formal registration, a single, intravenous infusion of BMS-188667 will be administered. Each formal registered subject will receive multiple doses after the transition period following a single dose. Each subject will receive one dose (Single-Day 1) during the single dose phase and 4 doses (Multiple- Days 1, 15, 29, and 57) during the multiple dose phase. After all subjects receiving BMS-188667 within each dose level have completed the single dose phase, data on safety and tolerability from these subjects will be examined according to set safety criteria before initiation of the multiple dose phase of the study and enrollment of another set of 7 subjects into the next higher dose level. If there are no safety problems, the multiple dose phase will be initiated where BMS-188667 will be administered to the same subjects from the single dose phase.	

<p>Study Population: Subjects with active rheumatoid arthritis of functional class I, II, or III who are diagnosed more than 6 months ago and are currently being treated with DMARDs (antirheumatic drugs) or immunosuppressants.</p>
<p>Test Product, Dose and Mode of Administration, Duration of Treatment: BMS-188667 (2, 8, and 16 mg/kg) will be infused intravenously in 30 minutes on Single-Day 1 (single dose phase) and on Multiple-Days 1, 15, 29, and 57 (multiple dose phase).</p>
<p>Reference Therapy, Dose and Mode of Administration, Duration of Treatment (Batch Numbers): Not applicable.</p>
<p>Criteria for Evaluation:</p> <ul style="list-style-type: none">• Safety Measures: Seriousness, Causal relationship to the study drug, Outcome, Action taken with respect to investigational product administration, Treatment required• Pharmacokinetic Measures: Cmax, Cmin, Tmax, AUC(INF), AUC(0-T), T-HALF, CLT, VSS, AI• Immunogenic Measures: anti-CTLA4Ig antibody, anti-CTLA4 antibody, immunogenicity response (positive/negative)• Efficacy Measures: ACR core data set components• Pharmacodynamic Measures: CRP, TNF-α, s-IL-2R, IL-6, MMP-3, RF
<p>Statistical Methods:</p> <ul style="list-style-type: none">• Safety Analyses: Significant physical examination findings, and clinical and laboratory tests will be listed. Summary statistics will be tabulated. Frequency distribution and individual listing of all adverse events will be generated. Marked abnormalities in clinical laboratory tests, changes from baseline will be listed. According to the dose, single dose phase/multiple dose phase, these data will be listed or tabulated as well as above.• Pharmacokinetic Analyses: Summary statistics will be tabulated for the pharmacokinetic parameters by dose and study day. To describe the dependency on dose for Cmax and AUC, scatter plots of these parameters versus dose after the single dose on Day 1, and after the last multiple dose on Day 57 will be provided. The distribution of Cmin concentrations will be summarized using descriptive statistics by dose and study day.• Immunogenicity Analyses: The distribution of immunogenic variables will be summarized using descriptive statistics by doses and time (single dose phase/multiple dose phase). The rate of positive immunogenicity response (if any) will also be calculated by doses and time (single dose phase/multiple dose phase).• Efficacy Analyses: Each component of ACR core data set will be calculated at each time-point and changes from baseline will be calculated and summarized by descriptive statistics per group.• Pharmacodynamic Analyses: Each component of the pharmacodynamic parameters will be calculated at each time-point and changes from baseline will be calculated and summarized by descriptive statistics per group.

RESULTS

1 STUDY POPULATION

Summary of study population and disposition of subjects were showed as Figure 1 and Table 1.



SAD: Single Administration Dose
MAD: Multiple Administration Dose

Figure 1. Subject Population and Disposition Flowchart

Table 1a. Study Population and Reasons for Discontinuation for Single dose phase (SAD)

	Dose of Abatacept		
	2 mg/kg	8 mg/kg	16 mg/kg
Preliminary Registration	7	7	8
Formal Registration	7	7	6
Administration of Study Drug	6	7	6
Completed	6	7	6
Discontinued	1	0	2
Prior to first administration of study drug	1 ¹⁾		2 ²⁾
During Transition Period (after SAD-Day57)	2 ³⁾	1 ³⁾	0
Evaluable			
Safety	6	7	6
Efficacy	6	7	6
PK	6	7	6

¹⁾ Due to serious adverse event.

²⁾ Due to withdrawal of consent.

³⁾ Due to lack of efficacy

Table 1b. Study Population and Reasons for Discontinuation for Multiple dose phase (MAD)

	Dose of Abatacept		
	2 mg/kg	8 mg/kg	16 mg/kg
Total	7	6	6
Continuance from SAD	4	6	6
Newly registered from MAD	3		
Administration of Study Drug (at least once)	6	6	6
Completed	6	6	6
Discontinued	2	0	0
Prior to first administration of study drug	1 ¹⁾		
Disease aggravated	1		
Evaluable			
Safety	6	6	6
Efficacy	6	6	6
PK	6	6	6

¹⁾ due to a ineligible subject

2 Baseline Demographic Characteristics

The demographic characteristics were showed as Table 2a and 2b.

Table2a. Baseline Demographic Characteristics: Single dose phase (SAD)

		Dose of abatacept		
		2mg/kg	8mg/kg	16mg/kg
Total		6	7	6
Gender	Male		2	1
	Female	6	5	5
Age(yrs)	Mean	50.0	47.9	52.8
	Range	34 - 65	25 - 62	45 - 62
Weight (kg)	Mean	53.7	60.6	61.6
	SD	8.9	11.0	14.3
	Range	42.0 - 66.0	42.0 - 76.5	46.5 - 85.7
Duration of RA (yrs)	Mean	8.0	12.6	15.0
	SD	3.3	11.0	13.0
	Range	2.3 - 12.0	1.4 - 29.0	2.1 - 32.5
Classification of Functional Status	Class I			2
	Class II	5	7	4
	Class III	1		
Disease Classification Of Steinbrocker	Stage I			2
	Stage II	4	4	1
	Stage III		1	1
	Stage IV	2	2	2
Tender Joints	Mean	15.2	14.7	13.7
	SD	3.8	4.5	3.4
Swollen Joints	Mean	11.0	17.4	13.5
	SD	4.9	8.1	4.1
CRP (mg/dL)	Mean	4.4	4.0	3.3
	SD	3.6	2.1	1.8
Complications	- (non)	1		
	+ (Yes)	5	7	6
Previous history	- (non)	1	2	2
	+ (Yes)	5	5	4
Operation history	- (non)	6	5	4
	+ (Yes)		2	2
Allergy history	- (non)	3	2	4
	+ (Yes)	3	5	2
DMARDs	MTX	5	5	5
	Other than MTX	1	2	1
NSAIDs	+ (Yes)	6	7	6
Steroids	+ (Yes)	6	7	6

Table2b. Baseline Demographic Characteristics: Multiple dose phase

		Dose of abatacept		
		2mg/kg	8mg/kg	16mg/kg
Total		6	6	6
Gender	Male		2	1
	Female	6	4	5
Age(yrs)	Mean	52.2	46.3	52.8
	Range	34 - 65	25 - 62	45 - 62
Weight (kg)	Mean	55.1	61.4	61.6
	SD	8.0	11.9	14.3
	Range	48.5 - 67.8	42.0 - 76.5	46.5 - 85.7
Duration of RA (yrs)	Mean	9.7	13.5	15.0
	SD	4.5	11.7	13.0
	Range	2.3 - 15.0	1.4 - 29.0	2.1 - 32.5
Classification of Functional Status	Class I			2
	Class II	5	6	4
	Class III	1		
Disease Classification Of Steinbrocker	Stage I			2
	Stage II	3	3	1
	Stage III		1	1
	Stage IV	3	2	2
Tender Joints	Mean	15.8	13.8	13.7
	SD	5.8	4.2	3.4
Swollen Joints	Mean	9.8	17.5	13.5
	SD	3.5	8.9	4.1
CRP (mg/dL)	Mean	1.9	3.6	3.3
	SD	1.1	1.9	1.8
Complications	- (non)	1		
	+ (Yes)	5	6	6
Previous history	- (non)	1	2	2
	+ (Yes)	5	4	4
Operation history	- (non)	4	5	4
	+ (Yes)	2	1	2
Allergy history	- (non)	5	2	4
	+ (Yes)	1	4	2
DMARDs	MTX	5	5	5
	Other than MTX	1	1	1
NSAIDs	+ (Yes)			
Steroids	+ (Yes)	6	6	6

3 SAFETY RESULTS

3.1 Serious Adverse Events

SAEs were not reported in the single dose phase. One of 18 subjects who had at least one administration of study drug was reported subcutaneous haematoma as SAE in multiple dose phase. Case report of SAE was shown as Table 3.

Two subjects in 2 mg/kg reported SAEs prior to first administration of study drug. One was admitted to the hospital due to nasopharyngitis after formal registration, and discontinued the study. Another subject was developed enterogastritis, and admitted to the hospital after preliminary registration. The enterogastritis was recovered after 7days, and the study was continued.

Table3. Case Report of Serious Adverse Event

Dose of abatacept	2 mg/kg
Serious Adverse Events (PT, MedDRA ver.8)	Subcutaneous haematoma
On set of event	53 days on multiple dose phase
Severity	Moderate
Taken action for study drug	Interruption (A-week postponement on forth administration)
Treatment to event	Yes (see below)
Outcome	Recovered
Duration of event	75 days
Relationship to study drug	Not related
Seriousness	Requiring inpatient hospitalization or prolongation of existing hospitalization
Progression	<p><u>October 9th, 2004:</u> The patient had a subcutaneous hematoma on bruise region of his right leg. Subcutaneous hematoma got enhanced and the patient visited hospital. A needle puncture was performed, and the red-colored fluids were only seen. Though no clear sign of infection was evidenced, the patient was admitted to the hospital by way of precaution. The antibiotic (fulmarin [flomoxef sodium], 1 - 2 g/day) was administered from October 9th to October 12th.</p> <p><u>October 13th - October 16th, 2004:</u> Oral Xaflor (norfloxacin, 400mg/day) was administered. The administration of Abatacept was initially planned at October 13th. However its postponed at October 21th due to subcutaneous hematoma.</p> <p>During admission, the region of subcutaneous hematoma was also disinfect by antiseptic solution (Osvan 0.02%) from October 9th to October 23th.</p> <p><u>October 27th, 2004:</u> Subcutaneous hematoma was not recovered, and started to treat by medical application (Sofratulle [fradiomycin sulfate] quarter square part of a medical application as every treatment).</p> <p><u>Novemver 4th, 2004:</u> Subcutaneous hematoma was only crust formation, and was continued by treatment of medical application.</p> <p><u>December 22th, 2004:</u> The crust was formed only 1-square centimeter. Medical application was discontinued.</p>

Relationship to study drug	<p>Not related.</p> <p>Since the adverse event reports on “Thrombocytopenia”, etc. have been made on the concomitant drugs [loxoprofen, methylprednisolone, indomethacin, methotrexate and cimetidine] , the drug relation of the drugs to the event could not fully be denied. However, on the concerned adverse event, the long term morbidity of the primary disease has weakened the peripheral blood vessels and the strong impact (bruise) likely resulted in the occurrence of adverse event and thus the drug relation to the study drug was evaluated “Not Related after re-reviewing the case.</p>
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3.2 Adverse Events

Adverse events (AE) profile was listed from Table 4a to Table 4d.

Table 4a. Adverse Events: in Single dose phase (SAD)

System Organ Class	PT	2mg/kg (n=6)		8mg/kg (n=7)		16mg/kg (n=6)		Total
		Relationship to study drug						
		Yes	No	Yes	No	Yes	No	
Cardiac disorders	Arrhythmia			1				1
Gastrointestinal disorders	Constipation		1					1
General disorder and administration site conditions	Malaise		1				1	2
	Thirst		1					1
	Nasopharyngitis	1		2			1	4
Infections and infestations	Herpes zoster			1				1
	Blood pressure increased		1	2	2	2	1	8
Investigations	Blood pressure diastolic increased				1			1
	Blood pressure systolic increased				1	1		2
	Heart rate increased					2		2
	Anorexia		1					1
Metabolism and nutrition disorders	Neck pain		1					1
Musculoskeletal and connective tissue disorders	Dysgeusia	1						1
Nervous system disorders	Hypoaesthesia			2				2
	Insomnia	1						1
Psychiatric disorders	Pharyngeal erythema		1					1
Respiratory, thoracic and mediastinal disorders	Seborrhoeic dermatitis		1					1
Skin and subcutaneous tissue disorders	Eczema asteatotic			1				1
	Pruritus				1			1
	Psoriasis			1				1
	Purpura			1				1
	Contusion						1	1
Injury, poisoning and procedural complications		3	8	11	5	5	4	36
Total								

The adverse event was garded as follows.

Related to study drug (Yes): "1. Certain ", "2. Probable" or "3. Possible"

Not Related to study drug (No): "4. Not likely" or "5. Unrelated".

MedDRA ver.8

Table 4b. Adverse Events of Clinical Laboratory in Single dose phase (SAD)

LLT	2mg/kg (n=6)		8mg/kg (n=7)		16mg/kg (n=6)		Total
	Relationship to study drug						
	Yes	Yes	Yes	Yes	Yes	Yes	
White blood cell count increased	1		2	1	3		7
Lymphocyte count decreased	2		2	1	1		6
Hb decreased				1			1
Platelet count increased					1		1
ALT increased		1					1
Cholesterol total increased			1	1	3		5
Creatinine serum increased					1		1
Blood phosphate decreased			1				1
Urine WBC increased			4		2		6
Urine RBC increased						1	1
Protein urine positive					2		2
Glucose urinary present					1		1
Ketone bodies urine positive		1		1			2
Urinary occult blood positive					1		1
Total	3	2	10	5	15	1	36

The adverse event was garded as follows.

Related to study drug (Yes): "1. Certain ", "2. Probable" or "3. Possible"

Not Related to study drug (No): "4. Not likely" or "5. Unrelated".

MedDRA ver.8

Table 4c. Adverse Events of Clinical Laboratory in Multiple dose phase (MAD)

SOC	PT	2mg/kg (n=6)		8mg/kg (n=6)		16mg/kg (n=6)		Total
		Relationship to study drug						
		Yes	No	Yes	No	Yes	No	
Cardiac disorders	Arrhythmia		1					1
	Cardiomegaly			1				1
Eye disorders	Astigmatism		1					1
	Cataract		1					1
	Vision blurred		1					1
	Keratitis						1	1
Gastrointestinal disorders	Stomach discomfort	1						1
	Stomatitis	1				2		3
	Vomiting		1					1
	Abdominal pain			1				1
General disorders and administration site conditions	Pyrexia	1						1
Infections and infestations	Cystitis	1						1
	Nasopharyngitis	3						3
	Gastroenteritis			1				1
	Vaginitis bacterial	1						1
	Pharyngitis					1		1
Injury, poisoning and procedural complications	Subcutaneous haematoma ¹⁾		1 ¹⁾					1 ¹⁾
	Contusion						1	1
	Excoriation						1	1
Investigations	Blood pressure increased	2		2			1	5
	Blood pressure diastolic increased			2				2
	Blood pressure systolic increased	3		2		2		7
	Heart rate increased						1	1
Nervous system disorder	Hypoaesthesia			1				1
	Headache		1					1
Psychiatric disorders	Insomnia	1						1
Respiratory, thoracic and mediastinal disorders	Sputum retention		1					1
	Pharynx discomfort					1		1
	Rheumatoid lung					1		1
Skin and subcutaneous tissue disorders	Hyperkeratosis				1			1
	Rash						1	1
Total		14	8	10	1	7	6	46

1)SAE

The adverse event was garded as follows.

Related to study drug (Yes): "1. Certain ", "2. Probable" or "3. Possible"

Not Related to study drug (No): "4. Not likely" or "5. Unrelated".

MedDRA ver.8

Table 4d. Adverse Events of Clinical Laboratory in Multiple dose phase (MAD)

LLT	2mg/kg (n=6)		8mg/kg (n=6)		16mg/kg (n=6)		Total
	Relationship to study drug						
	Yes	No	Yes	No	Yes	No	
White blood cell count increased			1		1		2
Neutrophil count increased	1						1
Lymphocyte count decreased	1			1	1		3
Hb decreased	1						1
Glucose blood level increased						1	1
AST increased		1					1
ALT increased		1					1
GGTP increase					1		1
Cholesterol total increased		1	1	1	3		6
Protein urine positive					1		1
Urine sugar positive						1	1
Ketone bodies urine positive		1					1
Urinary occult blood positive	1						1
Urine RBC increased	1				1	1	3
Urine WBC increased	3		1	1	1		6
Total	8	4	3	3	9	3	30

The adverse event was garded as follows.

Related to study drug (Yes): "1. Certain ", "2. Probable" or "3. Possible"

Not Related to study drug (No): "4. Not likely" or "5. Unrelated".

MedDRA ver.8

4 EFFICACY RESULTS

ACR response rate at Day 57 of single dose phase and at Day85 of multiple dose phase were shown as Figure 2 and Table 5.

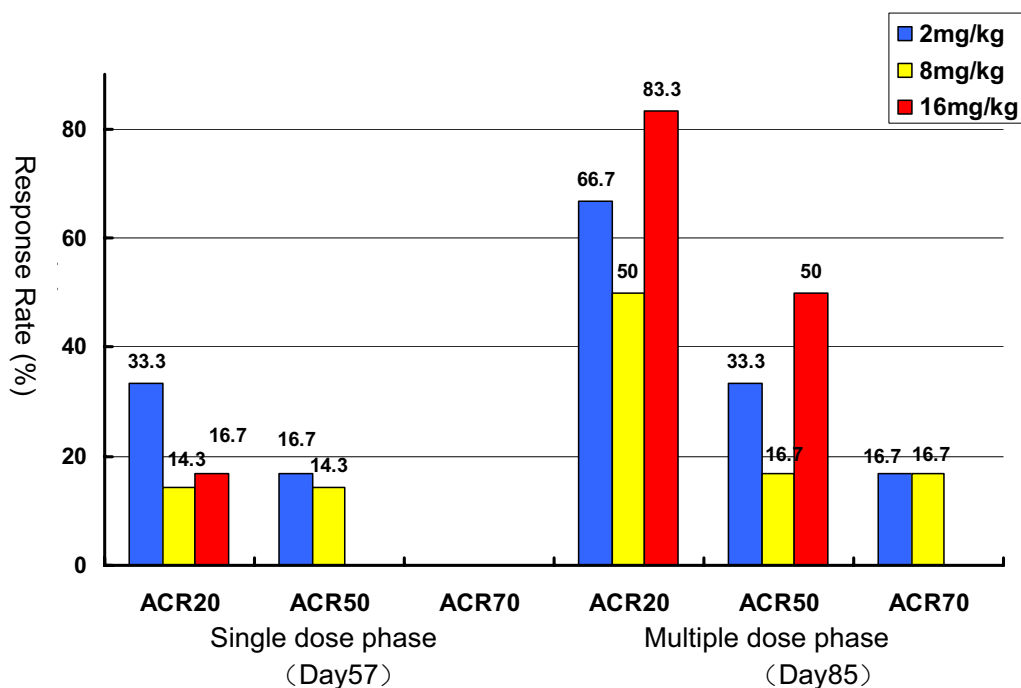


Figure 2. ACR Response Rate

Table 5. ACR Response Rate

	Single dose phase (Day57)			Multiple dose phase (Day85)		
	ACR20	ACR50	ACR70	ACR20	ACR50	ACR70
2mg/kg	33.3% (n=2/6)	16.7% (n=1/6)	0% (n=0/6)	66.7% (n=4/6)	33.3% (n=2/6)	16.7% (n=1/6)
8mg/kg	14.3% (n=1/7)	14.3% (n=1/7)	0% (n=0/6)	50.0% (n=3/6)	16.7% (n=1/6)	16.7% (n=1/6)
16mg/kg	16.7% (n=1/6)	0% (n=0/6)	0% (n=0/6)	83.3% (n=5/6)	50.0% (n=3/6)	0% (n=0/6)

5 PHARMACOKINETICS RESULTS

The pharmacokinetic profiles of BMS-188667 were assessed in totally 21 Japanese subjects with rheumatoid arthritis. BMS-188667 was administered at 2, 8, and 16 mg/kg as 30-minute IV infusions. The pharmacokinetic data from 21 subjects in total (19 subjects in the single dose phase and 18 subjects in the multiple dose phase) were available to evaluate the pharmacokinetic profiles of BMS-188667.

BMS-188667 demonstrated dose proportional pharmacokinetics in both the single and the multiple dose phases. Summary statistics of BMS-188667 pharmacokinetic parameters after single and multiple dose are given in Table 6 and 7, respectively. C_{max} values of BMS-188667 after single and multiple dosing at the dose range of 2-16 mg/kg were 36.41-318.01 µg/mL and 43.49-454.42 µg/mL, respectively. AUC(INF) values of BMS-188667 after single dosing were 4508.18-46063.43 µg·h/mL and AUC(0-T) values after multiple dosing were 6714.50-69918.13 µg·h/mL. No significant different were seen for T_{max}, T-HALF, CLT and V_{ss} between the single and the multiple dose phases, and each doses of 2-16 mg/kg. CLT values of the multiple dose phase (0.23-0.32 mL/h/kg) were smaller than those of the single dose phase (0.37-0.46 mL/h/kg). T-HALF values of BMS-188667 after single and multiple dosing were 211.93-246.55 h (8.8-10.3 days) and 231.66-304.51 h (9.7-12.7 days), respectively. V_{ss} values of BMS-188667 after single and multiple dosing were 0.10-0.12 L/kg and 0.08-0.11 L/kg, respectively, suggesting that BMS-188667 is confined primarily to the extra cellular fluid volume. Accumulation index (AI) calculated using AUC(TAU) after single dosing and multiple dosing was 1.39 to 1.92, thus, indicating minimal accumulation following multiple dosing

Table 6. Summary of Pharmacokinetics Parameters in Single-Dose Periods

Dose (mg/kg)	C _{max} ^a (µg/mL)	AUC(0-T) ^{a,d} (µg·h/mL)	AUC(INF) ^{a,e} (µg·h/mL)	T _{1/2} ^b (h)	T _{max} ^c (h)	CLT ^b (mL/h/kg)	V _{ss} ^b (L/kg)
2 (n=6)	36.41 (24)	4088.87 (30)	4508.18 (36)	211.93 (77.43)	1.25 (0.5, 2)	0.46 (0.15)	0.11 (0.02)
8 (n=7)	161.35 (14)	19295.20 (20)	21330.72 (23)	227.25 (63.15)	0.52 (0.5, 2)	0.38 (0.09)	0.10 (0.02)
16 (n=6)	318.01 (43)	39819.42 (48)	46063.43 (44)	246.55 (107.11)	2 (0.5, 2)	0.37 (0.16)	0.12 (0.06)

a Geometric mean (CV %)

b Arithmetic mean (SD)

c Median (min, max)

d Area under the serum concentration-time curve from time zero to Day 28

e Area under the serum concentration-time curve from time zero extrapolated to infinite time

Table7. Summary of Pharmacokinetics Parameters in Multiple-Dose (Day 57)

Dose (mg/kg)	C _{max} ^a (µg/mL)	AUC(0-T) ^{a,d} (µg·h/mL)	T _{1/2} ^b (h)	T _{max} ^c (h)	CLT ^b (mL/h/kg)	V _{ss} ^b (L/kg)	AI ^b
2 (n=6)	43.49 (21)	6714.50 (35)	304.51 (121.34)	1.27 (0.5, 6)	0.32 (0.10)	0.11 (0.02)	1.39 (0.15)
8 (n=6)	187.54 (15)	27270.04 (37)	231.66 (56.96)	1.25 (0.5, 2.17)	0.31 (0.10)	0.09 (0.02)	1.50 (0.86)
16 (n=6)	454.42 (28)	69918.13 (18)	264.89 (99.05)	2 (0.5, 2)	0.23 (0.04)	0.08 (0.02)	1.92 (0.77)

a Geometric mean (CV %)

b Arithmetic mean (SD)

c Median (min, max)

d Area under the serum concentration-time curve from time zero to Day 28

e AI = AUC(0-T) on Day 57 / AUC(0-T) on Day 1

6 IMMUNOGENICITY RESULTS

The immunogenicity of abatacept at doses of 2, 8, or 16 mg/kg was evaluated following a single dose on Day 1 (prior to dosing), Day 57, and at approximately 4 months after the single dose (just prior to first dose in the multi-dose phase of the study). During the multi-dose phase of the study, immunogenicity was evaluated on Days 1 (just prior to the first dose in the multi-dose phase) and 127 (70 days after the last dose in the multi-dose phase). Additional samples were also collected at the time of early discontinuation, as well as a few follow up or unscheduled collection time points. With the exception of 2 subjects in the 2 mg/kg-dose group and 1 subject in the 8 mg/kg-dose group, all patients continued into the multiple-dose phase. The 2 subjects in the 2 mg/kg-dose group that discontinued following the single dose were replaced by 2 new subjects in the multi-dose phase. All subjects who developed a positive antibody response to abatacept did so following the single dose and the response was directed to the CTLA4 portion of the molecule with titers ranging from 25 to 185. Of the 19 subjects treated with a single dose of abatacept none of the patients developed an antibody response by Day 57. However, 7 of the 19 subjects (37%) had developed an antibody response to abatacept, either following Day 57 and/or at the baseline for the multi-dose phase of the study (approximately 4 months following the single dose). The incidence of immunogenicity was inversely related to dose, with half of the subjects treated at the 2 mg/kg-dose level developing a response. Of the 18 subjects who entered the multi-dose phase, 5 subjects had a positive response at their baseline sample. However, following the multi-dose phase, all subjects (including the 5 positive at baseline) were negative for immunogenicity on Day 127, 70 days following the last dose. Thus, it is considered that immunogenicity was not enhanced by multiple dose of abatacept.

Table 8. Incidence of Positive Antibody Response to Abatacept^a

Dose Group	Single-Dose Phase		Multi-Dose Phase	
	By Day 57	By 4 months	Baseline	By Day 127 ^c
2 mg/kg ^b	0/6 0%	4/6 66%	2/6 33%	0/6 0%
8 mg/kg	0/7 0%	2/7 28%	2/6 33%	0/6 0%
16 mg/kg	0/6 0%	1/6 17%	1/6 17%	0/6 0%
Total	0/19 0%	7/19 37%	5/18 28%	0/18 0%

- a All responses directed to the CTLA4 portion of the molecule.
- b Three patients discontinued after the single-dose phase, 2 in 2 mg/kg-dose group and 1 in the 8 mg/kg-dose group. Two new patients were added to the 2 mg/kg-dose group for the multiple-dose phase.
- c 70 days following the last dose in the multi-dose phase.