Report on the Deliberation Results

May 6, 2010
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand Name]	Orencia for I.V. Infusion 250 mg
[Non-proprietary name]	Abatacept (Genetical Recombination) (JAN*)
[Applicant]	Bristol-Myers K.K.
[Date of application]	September 18, 2008

[Results of deliberation]
In the meeting held on April 23, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

[Conditions for approval]
The applicant is required to:

1. Conduct a drug use-results survey in all treated patients until data on a certain number of patients have been accumulated in order to collect data on the safety and efficacy of the product in the early post-marketing period, thereby taking necessary measures to ensure proper use of the product.

2. Conduct a large-scale post-marketing surveillance to thoroughly evaluate the safety of the product and to investigate the safety of long-term treatment with the product and the occurrences of infection, etc.

3. In order to confirm the efficacy (including the preventive effect on the progression of joint destruction) and safety of the product, conduct a double-blind comparative post-marketing clinical study using an appropriate control group.

**Japanese Accepted Name (modified INN)*

Review Report

April 8, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

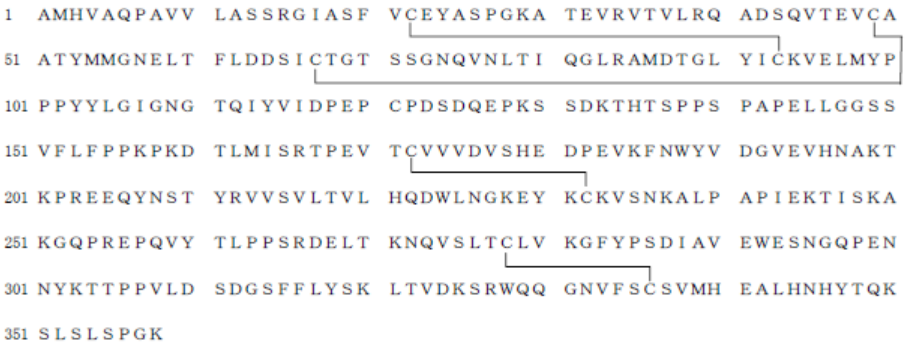
[Brand Name]	Orencia for I.V. Infusion 250 mg
[Non-proprietary name]	Abatacept (Genetical Recombination)
[Applicant]	Bristol-Myers K.K.
[Date of application]	September 18, 2008
[Dosage form/Strength]	Lyophilized product for intravenous infusion containing 250 mg abatacept in each 15-mL vial.
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	See Figures 1 to 3 below.

Molecular weight: approximately 92,000

Chemical name:

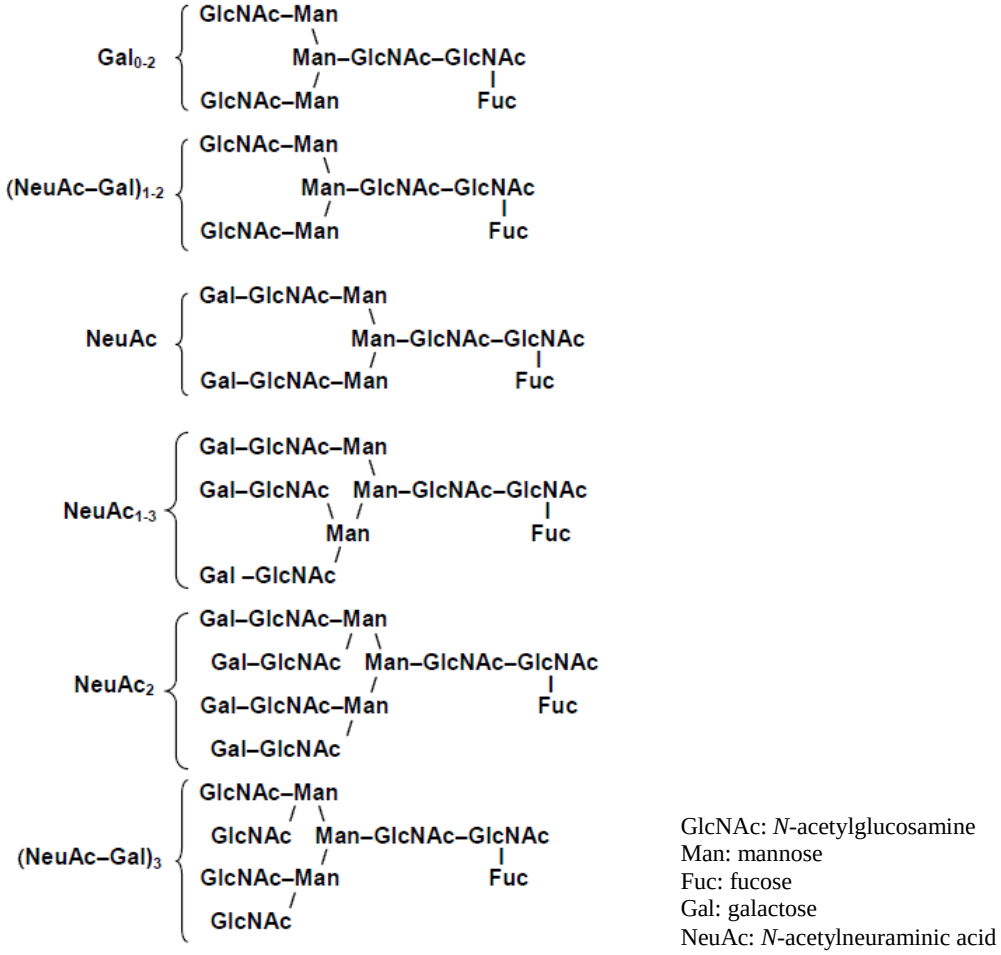
Abatacept is a recombinant fusion protein composed of the extracellular domain of human T-lymphocyte-associated antigen 4 at positions 1-125 and modified Fc domain of human IgG1 at positions 126-358, and whose amino acid residues at positions 131, 137, 140 and 149 are substituted by Ser. Abatacept is produced in Chinese hamster ovary cells. Abatacept is a glycoprotein (molecular weight: ca. 92,000) composed of 2 subunit molecules consisting of 358 amino acid residues each.

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV



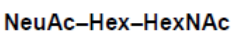
A1-D125: extracellular domain of CTLA-4
Q126-K358: modified Fc domain of human IgG1
S131, S137, S140, S149: modified amino acid residues
C121: inter-subunit disulfide bond
N77, N109, N208: *N*-linked glycans
S130, S140: *O*-linked glycans
A1: partial processing
K358: partial processing

Figure 1. Amino acid sequence of Abatacept (Genetical Recombination)



GlcNAc: *N*-acetylglucosamine
Man: mannose
Fuc: fucose
Gal: galactose
NeuAc: *N*-acetylneuraminic acid

Figure 2. *N*-linked glycans



Hex: hexose
HexNAc: *N*-acetylhexosamine

Figure 3. *O*-linked glycan

Review Results

April 8, 2010

[Brand Name] Orencia for I.V. Infusion 250 mg
[Non-proprietary name] Abatacept (Genetical Recombination)
[Applicant] Bristol-Myers K.K.
[Date of application] September 18, 2008
[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with rheumatoid arthritis has been demonstrated and its safety is acceptable in view of its observed benefits.

Serious adverse drug reactions such as infection have been reported to be associated with the product. It is therefore necessary to carefully assess the risks and benefits upon thorough observation of the patient's symptoms, etc., to fully inform the patient of the risks of the product, and to carefully monitor the clinical course of the patient after administration. After market launch, it is necessary to conduct a post-marketing surveillance to monitor all treated patients for adverse drug reactions, particularly serious infection, serious hypersensitivity, autoimmune diseases, etc., and also to conduct a long-term surveillance on infection, malignant tumors, etc. for further investigation. In addition, prevention of the progression of joint destruction should be clarified via a post-marketing clinical study.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration with the following conditions for approval.

[Indication] Rheumatoid arthritis (for use only in patients who have not adequately responded to conventional treatments)

[Dosage and administration] The usual adult dosage is the following dose of Abatacept (Genetical Recombination) administered by intravenous infusion. Abatacept is re-administered 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

Patient's body weight	Dose	Number of vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1 g	4

[Conditions for approval]
The applicant is required to:

(1) Conduct a drug use-results survey in all treated patients until data on a certain number of patients have been accumulated in order to collect data on the safety and efficacy of the product in the early post-marketing period, thereby taking necessary measures to ensure proper use of the product.
(2) Conduct a large-scale post-marketing surveillance to thoroughly evaluate the safety of the product and to investigate the safety of long-term treatment with the product and the occurrences of infection, etc.
(3) In order to confirm the efficacy (including the preventive effect on the progression of joint destruction) and safety of the product, conduct a double-blind comparative post-marketing clinical study using an appropriate control group.

Review Report (1)

March 3, 2010

I. Product Submitted for Registration

[Brand Name] Orencia for I.V. Infusion 250 mg
[Non-proprietary name] Abatacept (Genetical Recombination)
[Applicant] Bristol-Myers K.K.
[Date of application] September 18, 2008
[Dosage form/Strength] Lyophilized product for intravenous infusion containing 250 mg abatacept in each 15-mL vial.
[Proposed indication] Rheumatoid arthritis (for use only in patients who have not adequately responded to conventional treatments)
[Proposed dosage and administration]
The usual adult dosage is the following dose of Abatacept (Genetical Recombination) administered by intravenous infusion. Abatacept is re-administered 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

Patient's body weight	Dose	Number of vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1 g	4

II. Summary of the Submitted Data and Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Abatacept (Genetical Recombination) (hereinafter referred to as abatacept), the active ingredient of the product, is a soluble recombinant fusion protein manufactured by Bristol-Myers Squibb (USA). It is expressed in Chinese hamster ovary (CHO) cell lines genetically transfected with cDNA prepared by fusion of the cDNA encoding the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the cDNA encoding the Fc domain of human immunoglobulin G1 (IgG1). Abatacept specifically binds to CD80 and CD86 on the surfaces of antigen-presenting cells, thereby selectively inhibiting the co-stimulatory signal provided by the interaction between CD80/86 and CD28, and ultimately leading to suppression of T-cell activation. Therefore, with the expectation that abatacept would be useful for treating autoimmune diseases, development of the product as a therapeutic agent for rheumatoid arthritis (RA) was undertaken.

In foreign countries, clinical development of abatacept was started in 19[redacted]. The product was first approved for the indication of RA in the US in December 2005 and, as of March 2010, it has been approved for the indication of RA in not less than 50 countries or regions and for the indication of juvenile idiopathic arthritis in not less than 20 countries or regions as well.

In Japan, the clinical development of abatacept for RA was initiated in February 2004. The applicant conducted a Japanese phase II study (IM101-071) as a bridging study as per the ICH E5 Guideline. Based on the judgment that the data from foreign clinical studies can be extrapolated to Japanese patients, marketing application for abatacept for the indication of RA has now been filed.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Abatacept is a recombinant fusion protein composed of CTLA-4 at positions 1 to 125 and modified Fc domain of human IgG1 at positions 126 to 358, and whose amino acid residues at positions 131, 137, 140, and 149 are substituted by Ser. Abatacept is a glycoprotein (molecular weight: ca. 92,000) composed of 2 subunit molecules consisting of 358 amino acid residues each, which are produced by CHO cells.

2.A.(1).1) Manufacturing process

(a) Establishment of cell bank system

A DNA fragment encoding the extracellular domain of CTLA-4 was cloned from cDNAs of the HTLV II-infected T-cell leukemia H38 cell line. A signal sequence for oncostatin M secretion was bound to the upstream portion of the cDNA fragment and a DNA fragment encoding the Fc domain of human IgG1 was bound to the downstream portion of the cDNA fragment to prepare a DNA fragment encoding a fusion protein composed of CTLA-4 and Fc domain (CTLA4Ig). Then, the DNA fragment encoding CTLA4Ig was introduced into the downstream of [redacted] promoter in the [redacted] vector, and the DNA fragment encoding [redacted] and the DNA fragment containing the [redacted] promoter that expresses it were introduced to establish a gene expression construct [redacted]CTLA4Ig.

[redacted]CTLA4Ig was introduced into the CHO-[redacted] cell line by electroporation, and cells were selected in a medium containing fetal bovine serum (FBS) using the CTLA4Ig production level as the index. The primary cell line ([redacted]) was selected from these cells by methotrexate (MTX) using cell growth activity and the CTLA4Ig production level as indices. This [redacted] was conditioned to a chemically defined medium not containing components of animal origin ([redacted] medium) to select a manufacturing cell line ([redacted]) using cell growth activity, the CTLA4Ig production level, and sialic acid content as indices. A research cell bank (RCB) was prepared from this [redacted], and a master cell bank (MCB) was prepared from the RCB, and then a working cell bank (WCB) was prepared from the MCB.

(b) Characterization and control of cell banks

Purity tests (Table 1) and characterization (Table 2) have been conducted on the MCB, WCB, and the end-of-production cell bank (EPCB) that were cultured up to [redacted] passages after culturing.

Table 1. Purity tests of cell banks

Tests	Results		
	MCB	WCB	EPCB
	[redacted]29A-01	[redacted]30A-01, 22A-01, 88, [redacted]07, 30, [redacted]50, 49	Lot [redacted]44 (Process F)
Sterility test (direct inoculation method)	Complies	Complies	Complies
Bacterio-/myco-static test (direct inoculation method)	No bacterio- or myco-static activity	NT	No bacterio- or myco-static activity
Mycoplasma testing (culture method, indicator cell culture method)	Negative	Negative	Negative
Safety evaluation of test sample for mycoplasma testing	NT	NT	No mycoplasma-static effect, and cell growth in agar or liquid media, or Vero cell media was not inhibited.

Table 1. Purity tests of cell banks

Adventitious virus test	*In vitro* virus free test[1)]		Not detected	Not detected	Not detected
	In vivo latent virus free test Test animals: inoculated into mature mice, guinea pigs, and suckling mice		No contamination by adventitious virus detected	No contamination by adventitious virus detected	No contamination by adventitious virus detected
	In vivo murine antibody production (MAP) test		None of 16 species of viruses tested were detected. [2)]	NT	None of 17 species of viruses tested were detected. [3)]
	In vivo hamster antibody production (HAP) test[4)]		None of 5 species of viruses tested were detected.	NT	None of 5 species of viruses tested were detected.
	In vitro bovine virus free test		None of 5 species of viruses tested were detected. [5)]	NT	None of 9 species of viruses tested were detected. [6)]
	In vitro porcine virus free test		No porcine parvovirus was detected in [redacted].	NT	Not detected. Index cell line: [redacted]
	Murine minute virus (MMV) free test		Not detected by PCR	NT	Not detected by *in vitro* test
Infectious retrovirus test	Transmission electron microscopy	Cell culture	No virus-like particles other than retrovirus-like particles were observed.	NT	No virus-like particles other than retrovirus-like particles were observed.
		Cell culture supernatant	NT	NT	No virus-like particles other than retrovirus-like particles of [redacted]×[redacted]/mL were observed.
	Extended mink S^+L^- focus assay		Negative	NT	NT
	Reverse transcriptase assay and mink S^+L^- focus assay in co-culture (mink [redacted] cell line and [redacted] cell line)		NT	NT	Negative
	Reverse transcriptase assay (Mg^{2+}- and Mn^{2+}-dependent activity)		Not detected	NT	NT
	Reverse transcriptase assay and DNA synthetase assay		NT	NT	Negative

NT: not tested
[redacted] cell line: porcine [redacted] cells
[redacted] cell line: human [redacted] cell line

1) Positive control viruses: parainfluenza virus type 3, measles virus, simian virus 5
Index cell lines: human diploid lung cells (MRC-5), African green monkey kidney cells (Vero), Chinese hamster ovary cells (CHO-K1)

2) Viruses tested: lymphocytic choriomeningitis virus, murine hepatitis virus, murine pneumonia virus, murine minute virus, Sendai virus, ectromelia virus, murine rotavirus, reovirus type 3, murine encephalomyelitis virus, murine adenovirus, polyomavirus, hantavirus, mouse thymic virus, mouse salivary gland virus, K virus, lactate dehydrogenase-elevating virus

3) Viruses tested: murine parvovirus in addition to those listed in [2)]

4) Viruses tested: lymphocytic choriomeningitis virus, simian virus 5**,** murine pneumonia virus, reovirus type 3, Sendai virus

5) Viruses tested: bovine diarrhea virus, bovine adenovirus 5, bovine parvovirus, infectious bovine rhinotracheitis virus, bovine parainfluenza virus 3

6) Viruses tested: bluetongue virus, bovine respiratory syncytial virus, reovirus type 3, and rabies virus in addition to those listed in [5)]

Table 2. Characterization of cell banks

Parameters (test method)	Results		
	MCB	WCB	EPCB
	29A-01	22A-01, 88, 07, 30, 50, 49	Lot 44 (process F)
DNA sequence	Same as the expected base sequence	Same as the expected base sequence	Same as the expected base sequence
Insertion site of gene expression construct (Southern blotting)	A band indicting insertion was detected.	Same as the MCB band patterns	Same as the MCB band patterns
mRNA expression (Northern blotting)	A band indicting insertion was detected.	NT	Same as the MCB band patterns
DNA copy number/cell (Southern blotting)	About copies	NT	About copies
Identification and characterization of cultured cells (isozymes analysis[1)])	Hamster-derived	Hamster-derived	Hamster-derived

NT: not tested

1) Isozymes analyzed: , , , ,

The MCB is stored in a liquid nitrogen freezer outside the facility as well in preparation for emergency. The stability of the MCB under storage will be confirmed by stability tests (cell growth, microscopy) 1, 3, and 5 years after the start of cryopreservation, and every 5 years thereafter, according to the plan of the applicant. If the current MCB runs out of stock or fails to pass the stability tests, a new MCB will be prepared from the RCB according to the current preparation method, and the newly prepared MCB will be subjected to the current purity test and characterization.

The WCB will be renewed according to the current preparation method. The newly prepared WCB will be stored in a liquid nitrogen freezer, and subjected to cell growth tests (for cell viability after thawing, viable cell density of , cell viability after continuous culture for passages, viable cell density, and culture period) at hours and at months of storage, and every years thereafter. Cells thawed for WCB preparation will undergo the current purity test and characterization. They will also be checked for proliferative capacity on a small scale.

(c) Manufacturing process

The manufacturing process of abatacept is as follows.

The cell culture process through process are performed at (), and process and process at ().

Cell culture process

Cell thawing: WCB vial(s)
Medium: medium

Subculture
Medium: medium

Subculture 1
Equipment: cm^2 T flask

Subculture 2
Equipment: mL flask or L

In-process control tests

Cell viability after thawing

viable cell density, viable cell count, cell viability

viable cell density, viable cell density, cell viability

[redacted] bottle

Subcultures 3 and 4
Equipment: [redacted] or [redacted] L [redacted] bottle

Subcultures 5
Equipment: [redacted] L [redacted]

Subcultures 6 and 7
Equipment: [redacted] L [redacted]

- Subcultures [redacted] to [redacted] may [redacted] of [redacted].
- Subcultures [redacted] to [redacted] may [redacted].

[redacted] viable cell density, [redacted] viable cell density, [redacted] cell viability
[redacted] viable cell density, [redacted] cell viability, bioburden

[redacted] viable cell density, [redacted] cell viability
Bioburden (only for subculture [redacted])

Seed cell culture
Medium: [redacted] medium

Seed cell culture 1
Equipment: [redacted] kL bioreactor

Before culture: viable cell density, cell viability
During culture: [redacted]
After culture: viable cell density, cell viability, bioburden, endotoxin, [redacted] concentration, [redacted] concentration, [redacted] concentration, [redacted] concentration, [redacted]

Seed cell culture 2
Equipment: [redacted] kL bioreactor

Before culture: viable cell density, cell viability
During culture: [redacted]
After culture: viable cell density, cell viability, bioburden, endotoxin, [redacted] concentration, [redacted] concentration, [redacted] concentration, [redacted] concentration, [redacted]

Production culture
Medium: [redacted] medium
Supplemented media: [redacted] medium, [redacted] medium
Cell culture equipment: [redacted] kL bioreactor

Before culture: viable cell density, cell viability, endotoxin
During culture: [redacted], [redacted] viable cell density, [redacted] concentration
Before harvesting: bioburden, mycoplasma testing, *in vitro* adventitious virus free test
After culture: cell viability, [redacted], endotoxin, [redacted] concentration, [redacted] concentration, [redacted], content

Harvesting process
Equipment: [redacted], [redacted] membrane (pore size [redacted] to [redacted] µm, [redacted] to [redacted] µm), [redacted] membrane (pore size [redacted] µm)
pH adjustment: [redacted] mol/L [redacted] solution

In the harvesting container: content, bioburden, endotoxin
Before and after pH adjustment: pH

Purification process

[redacted] ion exchange chromatography
Equipment: [redacted] column

Before loading: bioburden, [redacted]
During elution: [redacted]
After elution: content, [redacted], [redacted], high molecular weight species, HCP, bioburden, endotoxin

Hydrophobic interaction chromatography
Equipment: [redacted] column

During elution: absorbance of eluted fractions
After elution: [redacted], high molecular weight species, DNA, HCP, [redacted], bioburden, endotoxin

Concentration
Equipment: Ultrafiltration membrane (exclusion molecular weight, [redacted] kDa)

After concentration: content, [redacted], high molecular weight species, bioburden, endotoxin

Viral inactivation
([redacted]% to [redacted]% [redacted] for [redacted] min at [redacted]°C to [redacted]°C)
Equipment: storage container

In-process: [redacted]
After process: bioburden, endotoxin

Affinity chromatography
Equipment: [redacted] column
pH adjustment: [redacted] mol/L [redacted] buffer (pH [redacted])

After elution: content, [redacted], high molecular weight species, DNA, HCP, [redacted], [redacted], [redacted], bioburden, endotoxin
Before and after pH adjustment: pH

Concentration and filtration I
Equipment: ultrafiltration membrane (exclusion molecular weight, [redacted] kDa)

After filtration: abatacept concentration, [redacted], bioburden, endotoxin

Viral filtration
Equipment: [redacted] (pore size [redacted]nm)

After filtration: abatacept concentration, bioburden, endotoxin

[redacted] ion exchange chromatography Equipment: [redacted] column	After elution: content, [redacted], high molecular weight species, DNA, HCP, [redacted], [redacted], [redacted], bioburden, endotoxin
Concentration and filtration II Equipment: Ultrafiltration membrane (exclusion molecular weight, [redacted] kDa)	In-process: [redacted], [redacted] After filtration: abatacept concentration, bioburden, endotoxin
Filling, storing, and transporting processes	
Filling Equipment: [redacted] membrane (pore size [redacted] μm) Filling container: [redacted] or [redacted] L PC bottle Storage: 2°C to 8°C, within [redacted] days	Bioburden, endotoxin
Freezing and cryopreservation Equipment: freezer at [redacted]°C to [redacted]°C Storage: [redacted]°C to [redacted]°C, from [redacted] hours up to [redacted] months	
Thawing and mixing/refrigerated storage Equipment: incubator ([redacted]°C to [redacted]°C), shaker for thawing, mixer Storage: 2°C to 8°C, within [redacted] days after filling	

- All processes are regarded as critical process steps. No critical intermediates are specified.
- Host cell-derived protein, HCP; host cell-derived DNA, DNA; CHO cell-derived [redacted] protein, [redacted]; polycarbonate, PC

The process validation of the manufacturing process for the drug substance has been performed on the commercial production scale.

In the culturing process, culture periods in [redacted] culture [redacted] and [redacted] culture [redacted] were investigated in addition to the above in-process control tests. The applicant claims that abatacept can be manufactured on a consistent basis by incubating the cells for <[redacted] hours in [redacted] culture [redacted], for ≤[redacted] hours in [redacted] culture [redacted], and by culturing the cells for [redacted] to [redacted] days in the production culture process, followed by harvesting cultured cells using [redacted] and [redacted] content of [redacted] as indices. In addition, [redacted] was confirmed in the harvesting process, from which the applicant claims that the consistency of the harvesting process is ensured.

Regarding the purification process, removal of process-related impurities and product-related impurities was evaluated. It was confirmed that the following impurities were sufficiently removed in a reproducible manner by the following chromatographic processes: high molecular weight species and host cell-derived protein (HCP) by hydrophobic interaction ([redacted] [redacted]) chromatography; [redacted], host cell derived DNA (hereinafter DNA), HCP, and CHO cell-derived [redacted] protein (hereinafter [redacted] protein) by affinity ([redacted] [redacted]) chromatography; and DNA and residual protein A by [redacted] ion exchange ([redacted] [redacted]) chromatography. The purification process is designed to proceed in a continuous manner. Based on the results of the stability test of intermediates, the applicant claims that the intermediate after harvesting can be stored for [redacted] days at [redacted]°C to [redacted]°C or for [redacted] days at [redacted]°C to [redacted]°C; the intermediate after viral inactivation for [redacted] days at [redacted]°C to [redacted]°C; and the intermediates after [redacted] ion exchange ([redacted] [redacted]), [redacted], [redacted], and [redacted] chromatography and the intermediate after viral filtration for [redacted] days at [redacted]°C to [redacted]°C.

Also, the load in [redacted], [redacted], and [redacted] chromatography processes and the yield in processes other than [redacted] chromatography were confirmed, from which the consistency of the yield of each process was confirmed. In addition, to assess [redacted] of virus filtration [redacted] and [redacted], investigation on a small scale and on a commercial scale, and characterization before and after [redacted] was conducted. As a result, the applicant claims that [redacted] can be performed up to [redacted]

time(s). The maximum number of reuse cycles of each column was investigated on a small scale and on the commercial production scale. Results showed that a consistent purifying capacity was maintained up to [redacted] times with [redacted], [redacted], and [redacted] columns and up to [redacted] times with [redacted] column.

The temperature, period, and mixing speed were examined for the freezing/cryopreservation process as well as the thawing and mixing/refrigerated storage process, and it was confirmed that the quality of the drug substance was comparable between before and after each process.

(d) Safety evaluation of adventitious infectious agents

i) Non-viral infectious agents

As raw materials of biological origin, [redacted] and recombinant human insulin are used in the cell culture process, dextran for the resin of the [redacted] column in the purification process, and recombinant protein A in [redacted] column. Recombinant human insulin is produced in yeast. Porcine pancreas-derived trypsin used in the process of insulin purification was derived from healthy animals and was heat-treated under acidic conditions and underwent acid treatment, thereby conforming to the Standards for Biological Materials. No animal-derived raw materials are used in the manufacturing process of [redacted], dextran or recombinant protein A.

ii) Adventitious viruses, etc.

Purity test was performed on the cell banks, and it was confirmed that they were not contaminated by bacteria, mycoplasmas, infectious retroviruses, or adventitious viruses (Table 1). In the cell culture process, mycoplasma testing and the *in vitro* adventitious virus free test are performed before harvesting. In the purification process, viral clearance test was performed. The results showed all model viruses tested to have been sufficiently removed (Table 3).

Table 3. Results of viral clearance test

Purification process	Viral reduction factor[1] (Log_{10})			
	A-MuLV	HSV-1	PPV	Reo-3
Viral inactivation ([redacted] treatment)[3]	[redacted]	[redacted]	NT	NT
[redacted] chromatography[2]	[redacted][4]	[redacted][4]	[redacted]	[redacted][4]
Virus filtration[3]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography[3]	[redacted][4]	[redacted]	[redacted][4]	[redacted][4]
Minimum total viral reduction factor[5]	>15.86	>17.51	>12.70	>17.18

NT, not tested

1) abelson murine leukemia virus; herpes simplex virus type 1; porcine parvovirus; reovirus type 3
2) Quantitative PCR
3) Infectivity assay ($TCID_{50}$)
4) Clearance value of reused resin
5) Sum of each clearance value

(e) Manufacturing process development (comparability)

During the establishment of the commercial scale manufacturing process for the drug substance (process F), the manufacturing process was changed 5 times (processes A, B, C, D, and E). The process D formulation was used up to the foreign phase II study, the process E formulation up to the foreign phase III and the Japanese phase I studies, and the process F formulation in the Japanese phase II and III studies.

Summary of changes are as follows.

- In process B, [redacted] process was added and the concentration of abatacept was changed from [redacted] mg/mL to [redacted] mg/mL.

- In process C, the scale of the production culture was increased from [redacted] L to [redacted] kL,

which was accompanied by the change in the harvesting method from [redacted] to [redacted]. Also, in order to effectively reduce bovine-derived [redacted], a component in the culture medium, [redacted] column and [redacted] column in the purification process were changed to [redacted] column, accompanied by the change of the timing of each process.

- In process D, [redacted] ion exchange ([redacted]) column, [redacted] column, and [redacted] column were added to reduce [redacted] protein.

- Up to process D, FBS of US bovine origin was used in preparing [redacted] that was used as the cell line for MCB preparation, and Primatone of US bovine origin was contained in the culture medium used in the preparation of MCB and WCB (cell bank) and in the manufacturing process. In process E, in order to reduce the risk caused by infectious factors, the seed cell line for MCB preparation was switched from [redacted] to [redacted] [see "2.A.(1).1) Manufacturing process, (a) Establishment of cell bank system"], and the medium for cell bank preparation and for the manufacturing process was switched from [redacted] medium containing Primatone to [redacted] medium. The purification process was optimized. Thus, [redacted] column and [redacted] column that had been added in process D were removed, and the timing of the process was changed. [redacted] column in [redacted] ion exchange chromatography in the [redacted] step was changed to [redacted] column.

- In process F, with the transfer of the production from [redacted] to [redacted], the scale of the production culture was changed to [redacted] kL, accompanied by the change of the harvesting method to centrifugation and [redacted]. Concentration/[redacted] process was added to the purification process.

In the evaluation of the comparability of the drug substance manufactured in each process, each drug substance was checked for conformity to specifications set during development and for the amount of process-related impurities remaining in each process (e.g., bovine-derived [redacted], recombinant human insulin, MTX, [redacted]).

The applicant explained that the comparability of the drug substance manufactured in processes D, E, and F was confirmed based on the results of the pharmacokinetic comparative studies in cynomolgus monkeys and humans (comparison between process D and process E, [redacted] and [redacted] studies; comparison between process E and process F, [redacted] and [redacted] studies), although the content of [redacted] ([redacted]) in process E and F drug substances slightly increased as compared with process D drug substance and the stability of process E and F drug substances and the drug product tended to differ slightly [see "3. Non-clinical data" and "4. Clinical data"].

2.A.(1).2) Characterization of drug substance

(a) Structure/Composition

The following tests were performed to characterize the drug substance.

i) Primary structure

(i) Amino acid composition

After acid hydrolysis of the drug substance, each amino acid was determined by reverse phase liquid chromatography (RPLC). The observed amino acid composition of abatacept was the same as the theoretical value estimated from the cDNA sequence.

(ii) Peptide mapping

After reduction-alkylation, trypsin peptides or Asp-N digested peptides separated by RPLC are analyzed by electrospray ionization-tandem mass spectrometry (ESI-MS/MS). The amino acid sequences were found to completely match the amino acid sequence estimated from the cDNA. It has also been confirmed by quadrupole time-of-flight mass spectrometry (qTOF-MS) that deamidation of Asn and Asn (≤ %) and oxidation of Met (≤ %) readily occurred.

(iii) N-terminal and C-terminal amino acid sequences

Edman degradation of the N-terminal peptide separated by RPLC showed the N-terminal amino acid sequence to be identical to that estimated from the cDNA sequence. Along with Met^{2}, Ala^{1} (about %) was identified as the N-terminal amino acid residue.

Peptide map and ESI-MS/MS of the C-terminal peptide separated by RPLC showed the C-terminal amino acid sequence to be identical to that estimated from the cDNA sequence. Along with Gly^{357}, Lys^{358} (%− %) was identified as the C-terminal amino acid residue.

(iv) Monosaccharide analysis: glycosylation site and glycan structure

Monosaccharide analysis has shown that each mole of abatacept contains to , to , to , to , to , to , and to moles of monosaccharides (mannose, galactose [Gal], fucose, *N*-acetylglucosamine, *N*-acetylgalactosamine [GalNAc]), and sialic acids (NeuAc, *N*-glycolylneuraminic acid [NeuGc]), respectively. These carbohydrates accounted for approximately % of abatacept by mass.

Regarding the sialic acid content of abatacept, pharmacokinetic studies in mice and cynomolgus monkeys (in which drug substances containing different volumes of sialic acid were administered) showed a positive correlation between the sialic acid content and the pharmacokinetics (AUC) and a negative correlation between the sialic acid content and the pharmacokinetics (clearance). It was also shown that content in abatacept increased in correlation with the amount of added to the supplemented medium in the production culture process, indicating the enhanced sialylation of abatacept.

N-linked glycans bind to Asn^{77}, Asn^{109}, and Asn^{208}, as shown by LC/MS of trypsin-digested peptides separated by RPLC.

Analysis of all *N*-linked glycans released by *N*-glycosidase (PNGase F) by high pH anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) has shown that asialo-, monosialo-, disialo-, and trisialo-forms are present in amounts of % to %, % to %, % to %, and % to %, respectively. In addition, analysis of each *N*-linked glycan confirmed that i) Asn is linked to biantennary to tetraantennary mono- or di-sialylated heterogeneous glycans, that ii) Asn is linked mainly to biantennary (and only slightly to triantennary and tetraantennary), mainly mono- and di-sialylated (and only slightly to asialylated or trisialylated) glycans, and that iii) Asn is linked to biantennary asialylated glycans and slightly to mono- and di-sialylated glycans.

Analysis of all *N*-linked glycans by porous graphitized carbon liquid chromatography and by qTOF-ESI-MS showed glycans to be similar to those identified by HPAEC-PAD, confirming the glycan structure and its molecular weight in each peak.

As for 2 *N*-linked glycans present in the CTLA-4 region, crystal structure analysis of the complex of the extracellular domain of CTLA-4 and CD80 or CD86 showed the existence range of the *N*-linked glycans to be distant from the binding interface of CTLA-4 and CD80 or CD86, precluding the possibility of involvement of the glycans in the recognition between CTLA-4 and

CD80 or CD86 (Schwartz et al. *Nature*. 2001;410: 604-608, Stamper et al. *Nature*. 2001;410: 608-611).

O-linked glycans bind to Ser^{130} and Ser^{140}, as demonstrated by LC-MS/MS and Edman degradation of trypsin-digested peptides separated by RPLC. In addition, analysis by electron transfer dissociation-MS/MS has confirmed presence of a slight amount of *O*-linked glycans in [redacted].

Analysis by ESI-MS/MS has confirmed that the major forms of glycans linked to Ser^{130} and Ser^{140} are HexNAc-Hex-NeuAc and [redacted]lated HexNAc-Hex-NeuAc. In addition, based on the detection of [redacted] and [redacted] by monosaccharide analysis of *O*-linked glycans by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), the major form of glycans linked to Ser^{140} is considered to be [redacted].

ii) Physicochemical properties

(i) Molecular weight

The molecular weight of the major peak from MALDI-TOF-MS was [redacted]±[redacted] Da, which was identical with the theoretical molecular weight.

(ii) Electrophoretic pattern

Isoelectric focusing (IEF) of abatacept showed [redacted] to [redacted] bands within pI range from [redacted] to [redacted].

SDS-PAGE (CBB staining) under non-reducing conditions showed that the main peak corresponded to a monomer of approximately 100 kDa and minor bands represented a non-covalently bound high molecular weight species of approximately 200 kDa (dimer), a subunit of approximately [redacted] kDa, and a small amount of a low molecular weight species of approximately [redacted] kDa. SDS-PAGE under reducing conditions showed the subunit as the main band and, as minor bands, a high molecular weight species (dimer) and a low molecular weight species.

(iii) Liquid chromatographic pattern

Analysis by size exclusion high performance liquid chromatography (SEC-HPLC) confirmed the main peak to be the monomer ([redacted]% to [redacted]%) and, minor peaks to represent a high molecular weight species (dimer) ([redacted]% to [redacted]%) and a small amount of a low molecular weight species (not more than the lower quantitation limit [[redacted]%]).

iii) Higher order structure

One mole of abatacept contains [redacted] to [redacted] moles of free thiol groups, as determined by Ellman's method.

Abatacept, with or without reduction, was digested by enzymes (trypsin, trypsin/chymotrypsin, or trypsin/elastase), and the peptides obtained were separated by RPLC. Those peaks that showed a difference between reduced and non-reduced abatacept were subjected to analysis by ESI-MS/MS. Results showed the presence of 4 intra-subunit bindings (Cys^{22}-Cys^{93}, Cys^{49}-Cys^{67}, Cys^{172}-Cys^{232}, Cys^{278}-Cys^{336}) and 1 inter-subunit binding (Cys^{121}-Cys^{121}).

It has been confirmed that abatacept has a minimum absorption at approximately [redacted] to [redacted] nm in the circular dichroism (CD). Crystal structure analysis has shown that the extracellular domain of CTLA-4 and Fc domain are rich in β-sheet structure (Stamper et al. *Nature.* 2001;410: 608-611, Deisenhofer et al. *Resolution Biochemistry*. 1981;20:2361-2370). Therefore, abatacept is not an antibody molecule, but its secondary structure is thought to be rich in β-sheet structure and similar to that of an antibody molecule with a minimum absorption at around 215 to 220 nm.

iv) Biological properties

(i) Analysis by surface plasmon resonance has shown that the dissociation constant (K_D), association rate constant (k_a), and dissociation rate constant (k_d) of abatacept with the fusion protein of CD80 and Fc region of IgG1 (B7Ig) were [redacted] nM, [redacted] $M^{-1}s^{-1}$, and [redacted] s^{-1}, respectively.

(ii) IL-2-inhibiting activity (EC_{50}) was found to be [redacted] μg/mL by IL-2 promoter-reporter luciferase assay.

(iii) Regarding the interactions between Fc region of abatacept and human Fc receptor or complements, no Fc-mediated activity of abatacept has been detected in the following tests.

- In a complement-dependent cytotoxicity test using a human [redacted] cell line expressing CD80 and CD86 ([redacted]), it was shown that abatacept have no complement-dependent cytotoxicity in the presence of rabbit, juvenile rabbit, guinea pig, or human complements.

- In an antibody-dependent cellular cytotoxicity test using PM-LCL, it was shown that abatacept have no antibody-dependent cellular cytotoxicity mediated by peripheral blood monocytes (PBMC).

- Analysis by flow cytometry and by surface plasmon resonance showed that, among immunoglobulin receptors (CD16, CD32, CD64) abatacept did not bind to CD16 or CD32 but bound to CD64. The binding, however, was shown to be weak compared to the binding activity of CTLA-4Fc (abatacept without amino acid substitutions in the hinge region, which has Fc-mediated activity).

(iv) The affinity of abatacept for the Fc receptor of neonates (FcRn) has been shown to be similar to that of human IgG1, as determined by surface plasmon resonance. The maximum binding capacity of abatacept was slightly lower than that of human IgG1. The extracellular domain of CTLA-4 in abatacept is corresponding to the Fab region (which is the region not directly involved in the binding with FcRn) in human IgG1, and it appears to have affected the conformation of the Fc region, resulting in the reduced binding capacity.

(b) Product-related substances

Presence of an N-terminal Ala adduct, a C-terminal Lys adduct, a Met oxidant, and an Asn-deamidated form have been confirmed by peptide mapping. Different glycoforms have been identified by monosaccharide analysis, glycosylation profile analysis, and IEF. Presences of a high molecular weight species (dimer) and a low molecular weight species have been confirmed by SDS-PAGE (CBB staining) under reducing and non-reducing conditions and by SEC-HPLC. Acceptable limits are defined for molecular species other than the N-terminal Ala adduct and C-terminal Lys adduct, and the levels of these molecular species are maintained below these limits within the product's shelf life.

Characterization of the high molecular weight species (dimer) showed that the IL-2-inhibiting activity and B7Ig-binding activity were higher than with the monomer. These increases were attributed to the increase in [redacted] due to the decrease in [redacted] between the high molecular weight species and [redacted].

A low molecular weight species generated by cleavage between [redacted] and [redacted] has been found.

(c) Impurities

i) Process-related impurities

It has been confirmed that host cell-derived impurities (DNA, HCP, MCP-1-like protein) and process-related impurities (MTX, recombinant human insulin, protein A, [redacted], heavy metals) are efficiently removed during the purification process. In addition, host cell-derived impurities, protein A, and heavy metals are included in the specifications for the drug substance.

ii) Product-related impurities

No product-related impurities have been detected during the manufacturing process or within the specified shelf life.

2.A.(1).3) Drug substance specification

The following tests are included in the specifications for the drug substance: description, identification (capillary electrophoresis [CE]), monosaccharide composition (amino monosaccharides, neutral monosaccharides) and sialic acid, glycosylation profile, IEF, peptide mapping, pH, purity tests (heavy metals, SEC-HPLC, SDS-PAGE (CBB staining) under reducing and non-reducing conditions, HCP, MCP-1-like protein, protein A, DNA, free thiol group), bacterial endotoxins, microbial limit test, B7Ig-binidng activity, IL-2-inhibiting activity, and assay (protein concentration).

2.A.(1).4) Stability of the drug substance

The following attributes were tested for the drug substance: appearance and clarity, color, IEF, peptide mapping, pH, SEC-HPLC, SDS-PAGE (CBB staining) under reducing and non-reducing conditions, B7Ig-binding activity, IL-2-inhibiting activity, protein concentration, bioburden, and bacterial endotoxins.

For the drug substance manufactured at [redacted], attesting was performed at the long-term stability condition (freezing) (-40°C, 36 months, 3 lots, [redacted]-L polycarbonate [PC] bottles), the long-term stability condition (5°C, 12 months, 3 lots [redacted]-mL PC bottles), and the accelerated condition (25°C/40% RH, 3 months, 3 lots, [redacted]-mL PC bottles) were performed. Results of the long-term testing demonstrated the stability of abatacept except for a slight increase over time in the high molecular weight species after storage at 5°C. In contrast, the accelerated testing showed a tendency for an increase in the high molecular weight species and for a decrease in the monomer.

For the drug substance manufactured at BMS, stress testing (photostability testing, repeated freeze-thawing test, forced degradation test) and additional tests (storage at 5°C or at 25°C/40% RH after the long-term storage [cryopreservation]) were performed. In the photostability testing (1 lot, [redacted]-mL PC bottles), abatacept was stable under room light both at 5°C for 4 weeks and at 25°C/60% RH for 1 week, whereas when exposed to light (25°C, 8 days, 1.2 million lux hours, 200 watt hours/m^2 [total illumination for 4 days]), tendencies for an increase in the high molecular weight species and for a decrease in the monomer, increases in minor bands on SDS-PAGE under reducing and non-reducing conditions, and an increase in IL-2-inhibiting activity were observed. Abatacept was stable in the light-resistant containers. Abatacept was also stable in the repeated freeze-thawing test ([redacted] cycles of [redacted]°C and [redacted]°C [[redacted] days each], 2 lots, [redacted]-mL PC bottles). In the forced degradation tests (under conditions of oxidative stress, light exposure, high temperature, low pH, high pH), the high molecular weight species was observed as the major product. In the additional study (1 lot), the test samples that had been stored at [redacted]°C for [redacted] months were further stored at [redacted]°C for [redacted] months ([redacted]-L PC bottles) or at

[redacted]°C/[redacted]%RH for [redacted] months ([redacted]-mL PC bottles). Abatacept was stable under both storage conditions except that [redacted] of [redacted] was observed at months [redacted] and [redacted] when stored at [redacted]°C. Since the [redacted] was not observed in 20 lots of the drug substance stored under the same condition, the applicant explained that it was a change observed only in the test lot.
For the description of the drug substance in the stability test, [redacted] was observed, independent of the storage period. Since this [redacted] is [redacted] used in the manufacturing process and for storage, and is removed in the sterile filtration process during formulation, the applicant explained that it does not affect the quality of abatacept. [1]

On the basis of the above results, the shelf life of the drug substance was determined to be [redacted] months at [redacted]°C to [redacted]°C and [redacted] days at 2°C to 8°C, when stored in PC bottles in a dark place. Freezing and thawing from [redacted]°C to [redacted]°C is thus allowed up to [redacted] times.

2.A.(2) Drug product

2.A.(2).1) Formulation development

Abatacept 250 mg for injection is a lyophilate for injection that contains, in each 15-mL vial, 250 mg abatacept (Genetical Recombination) as the active ingredient, 14.6 mg sodium chloride as the tonicity agent, 17.2 mg sodium dihydrogen phosphate monohydrate as the buffering agent, 500 mg maltose hydrate as the stabilizer, and an appropriate amount of hydrochloric acid or sodium hydroxide for pH adjustment. Each vial is overfilled by 5% beyond the nominal content. One 10-mL plastic syringe for reconstitution (manufactured by [redacted]) is attached.

During the process of development, the formulation was revised once. Based on the results of the study on the minimum amount of maltose required for the stabilization of abatacept, the mixing ratio of abatacept and maltose hydrate was changed from [redacted]:[redacted] to 1:2 from the formulation used in the foreign phase II study. In addition, the content of abatacept per vial was changed from 50 mg (6% overfill) to 200 mg (7.5% overfill) in the formulation for the foreign phase II study, then to 250 mg (5% overfill) in the formulation for the phase III study and in the commercial formulation.

From the foreign phase II study, dedicated syringes without silicone oil coating have been used for the reconstitution of the lyophilized product. During the early stage of the development, abatacept-derived particles formed probably as a result of interaction with silicon oil, which is commonly used as the lubricant for syringes. Syringes without silicon oil coating are used to avoid this phenomenon. Furthermore, an in-line filter is used when administering abatacept to control possible formation of particles observed during the early stage of development of abatacept [see 2.A.(2).4) Stability of drug product].

2.A.(2).2) Drug product formulation process

Maltose hydrate is added to the drug substance (already containing the tonicity adjusting agent and the buffering agent), the pH of the mixture is adjusted as necessary and the mixture is then diluted with water for injection to a final volume to obtain the bulk solution (solution preparation process). The bulk solution is sterility filtered through a [redacted] prefiltration membrane (pore size 0.45, 0.22 μm) and bipartite filtration membranes (pore size 0.22 μm) (sterile filtration process), and the filtrate is filled in 15-mL colorless glass vials, which are partially stoppered with sterile butyl rubber stoppers (filling process). After lyophilization, the vials are fully stoppered (lyophilization process) and sealed tightly with flip-off aluminum caps (sealing process). The stoppered vials are labeled, packaged together with dedicated syringes for reconstitution, and stored at 2°C to 8°C (labeling, secondary

[1] An in-line filter is used in administering Abatacept [see "2.A.(2). 4) Stability of drug product"].

packaging, testing, storage process). Critical processes in the formulation process are the solution preparation, sterile filtration, filling, and lyophilization processes. The following in-process control tests have been set: [redacted], [redacted], and [redacted] in the solution preparation process; bioburden and endotoxin before and after pre-filtration and membrane integrity test before and after sterile filtration in the sterile filtration process; sterility test at the start of filling and filling mass in the filling process; and CE, IEF, and IL-2-inhibiting activity after the sealing process.

Process validation is performed in each process, and it is confirmed that the sterile drug product is manufactured in a highly reproducible manner.

2.A.(2).3) Drug product specifications

The following tests were included in the specifications for the drug product: description, identification (peptide mapping), pH, osmotic pressure, purity test (clarity and color of solution, SEC-HPLC, SDS-PAGE [CBB staining] under reducing and non-reducing conditions), water content, bacterial endotoxins, sterility test, uniformity of dosage units, foreign insoluble matter test, insoluble particulate matter test, dissolution time, B7Ig-binding activity, and assay (protein concentration).

2.A.(2).4) Stability of drug product

The following attributes were tested for the drug product: appearance, CE, IEF, peptide mapping, pH, clarity and color of solution, SEC-HPLC, SDS-PAGE (CBB staining) under reducing and non-reducing conditions, water content, endotoxin test, sterility test, mass variation test, insoluble particulate matter test, dissolution time, B7Ig-binding activity, IL-2-inhibiting activity, and protein concentration.

For the drug product manufactured using the drug substance manufactured at [redacted], a long-term testing (freezing) (-20°C, 36 months, 3 lots), a long-term testing (5°C, 36 months, 3 lots), an accelerated testing (25°C/60% RH, 36 months, 3 lots), and stress testings (30°C/65% RH for 12 months, or 40°C/75%RH for 6 months, 3 lots each) were performed. Results of each long-term testing demonstrated the stability of abatacept. In contrast, the accelerated testing showed a tendency for an increase in the high molecular weight species, a tendency for a decrease in the monomer, and a tendency for an increase in IL-2-inhibiting activity, as well as minor bands in SDS-PAGE under reducing and non-reducing conditions from month [redacted], and new peaks in peptide mapping from month [redacted]. The stress testing at 30°C/65% RH showed a tendency for an increase in the high molecular weight species, a tendency for a decrease in the monomer, and a tendency for an increase in IL-2-inhibiting activity, as well as minor bands in SDS-PAGE under reducing and non-reducing conditions from month [redacted], and new peaks in peptide mapping from month [redacted]. The stress testing at 40°C/75% RH showed an increase in the high molecular weight species and a decrease in the monomer over time, as well as new peaks in peptide mapping from month [redacted], minor bands in SDS-PAGE under reducing and non-reducing conditions from month [redacted], and a tendency for an increase in IL-2-inhibiting activity from month [redacted].

For the drug product manufactured using the drug substance manufactured at [redacted], stress testing (photostability testing, repeated freeze-thawing test, forced degradation test) was performed. The photostability testing (20°C to 25°C, 4 days, 1 lot, 1.2 million lux hours, 200 watt hours/m^2 [total illumination for 4 days]) showed a tendency for an increase in the high molecular weight species and a tendency for a decrease in the monomer, as well as minor bands in SDS-PAGE under non-reducing conditions from Day [redacted]. The drug product was stable in a light-resistant container. Abatacept was also stable in the repeated freeze-thawing test ([redacted] cycles of [redacted]°C and

[redacted]°C/60% RH [[redacted] days each], 1 lot). In the forced degradation tests (oxidation, light exposure, high temperature, low pH, high pH), the high molecular weight species was observed as the major product. In addition, glycation of abatacept due to the stabilizer maltose was observed, but not within the proposed shelf life.

On the basis of the above results, the shelf life of the drug product was determined to be 36 months at 2°C to 8°C when stored in a dark place.

The drug product is diluted with water for injection or saline to a concentration of 25 mg/mL, followed by further dilution with saline. The following studies were conducted to evaluate the stability of abatacept upon reconstitution, and the compatibility between the reconstituted solution and the filter.

When the drug product (6 lots, 5°C, at manufacturing and after storage for [redacted] months, [redacted] years, or [redacted] years) was dissolved in water for injection or saline to a concentration of 25 mg/mL and the solution was stored for 24 hours at 5°C in a dark place or at room temperature (20°C to 25°C) under scattered room light (538-2153 lx), no marked change was observed in appearance, IEF (only for the product diluted with water for injection), pH, clarity and color of solution, SEC-HPLC, SDS-PAGE (CBB staining) under reducing and non-reducing conditions, dissolution time, insoluble particulate matter, B7Ig-binding activity, or protein concentration. Also, when the 25 mg/mL reconstituted solution was transferred to a bag for intravenous infusion (polyvinyl chloride bag or non-polyvinyl chloride bag), diluted with saline to a final concentration of 1 or 10 mg/mL, and stored for 24 hours at 5°C in the dark place or at room temperature under scattered room light, no marked change was observed in pH, SEC-HPLC, SDS-PAGE (CBB staining) under reducing and non-reducing conditions, B7Ig-binding activity, or protein concentration. On the basis of the above results, the applicant decided that if the reconstituted solution is stored for an unavoidable reason, it should be stored at 2°C to 25°C and be used within 24 hours.

When the reconstituted solution of the drug product was filtered through an in-line polyethersulfone filter (pore size 0.2 μm, 1.2 μm) commonly used in administering protein preparations, no change was observed in SEC-HPLC, B7Ig-binding activity, or protein concentration. Neither was adsorption of abatacept to the filter observed. When the bag containing 1 or 10 mg/mL reconstituted solution was stored for 24 hours at 5°C in a dark place or at room temperature under scattered room light, and the solution was then filtered through the filter, insoluble particulate matter was sufficiently removed. On the basis of the above results, the applicant decided that the reconstituted solution should be filtered through a sterile, pyrogen-free, low-protein-binding in-line filter with a pore size of 0.2 to 1.2 μm.

2.A.(3) Reference material

The current reference material is the drug substance (lot No. [redacted]) manufactured according to the manufacturing process of abatacept. It is stored at [redacted]°C. The reference material is qualified by specifications of the drug substance, characterization (N-terminal amino acid sequence, mass spectrometry [ESI-MS], IL-2-inhibiting activity [EC_{50}]), and comparability study with the current reference material (CE, glycosylation profile, IEF, peptide mapping, SDS-PAGE [CBB staining] under reducing and non-reducing conditions). The shelf life of the reference material is [redacted] months, and the re-test period is set at [redacted] years.

The reference material is renewed with consideration given to the shelf life and the remaining amount of the current reference material. A new lot of the drug substance is manufactured according to the same manufacturing process as used for the current reference material, and after being examined for the eligibility of the reference material, it is used in place of the current

reference material. Stability during the storage period is checked at [redacted] and [redacted] months after manufacturing and every [redacted] months thereafter by measuring the following parameters: description, glycosylation profile, IEF, peptide mapping, pH, SEC-HPLC, SDS-PAGE (CBB staining) under reducing and non-reducing conditions, free thiol group, B7Ig-binding activity, IL-2-inhibiting activity (EC_{50}), assay (protein concentration), and N-terminal amino acid sequence.

2.B Outline of the review by PMDA

PMDA performed the review of the submitted data including the following major evaluations and, as a result, concluded that the quality of the commercial drug product is controlled in an appropriate manner.

2.B.(1) Control of immunogenic glycans

Abatacept contains 3 immunogenic *N*-linked glycans containing NeuGc: two bound to the extracellular domain of CTLA-4 and one to the Fc region.

PMDA has concluded that there are no particular problems with the method for controlling the immunogenic glycans, for the following reasons: (a) the glycan structure and structural heterogeneity have been analyzed in the characterization of the drug substance (monosaccharide analysis, structural analysis of *N*-linked glycans) and, for monosaccharide composition (amino monosaccharides, neutral monosaccharides), sialic acid and glycosylation profile in the specifications for the drug substance, the contents of each monosaccharide and sialic acid and contents of asialo-, monosialo-, disialo-, and trisialo-forms are specified, and appropriately controlled, and (b) according to the results of abatacept administration so far available, expression of anti-abatacept antibody or anti-CTLA-4 antibody was reported in approximately 6.3% of patients (252 of 3985 subjects) in foreign clinical studies and in 14.3% (33 of 231 subjects) in Japanese clinical studies, but no relation was observed between the expression of the antibody and the incidence of adverse events, from which the applicant explained that the antibody is unlikely to affect the safety of abatacept [see "4.(ii).A.(4) Immunogenicity"].

2.B.(2) Drug product specifications

The identification (CE), IEF, and IL-2-inhibiting activity were included in the specifications for the drug product in the US and in Europe, but not in Japan. Therefore, PMDA asked the applicant to include these tests in the specifications to ensure the quality of the drug product to be marketed in Japan.

The applicant replied that these tests are not included in the specifications, for the following reasons: (a) CE was used to identify abatacept in the drug product during development, but it can be substituted by peptide mapping. In the US and Europe, application for removal of CE from the drug product specifications is planned, (b) among the drug product specifications, IEF is the only test that can detect the heterogeneity of molecular species with different electric charges. However, this test is inferior to other tests in detecting changes in abatacept. For example, test samples that fail to pass other tests often pass the IEF test. Therefore, application for removal of IEF from the drug product specifications is planned in the US and in Europe, and (c) although IL-2-inhibiting activity can evaluate the clinical efficacy of abatacept, it tends to vary because of its characteristics.

Also, the applicant explained as follows:
These tests are carried out as part of release tests for the drug product marketed in the US and Europe. Therefore, the quality of the drug product can be ensured by including these tests in the in-process control tests in the manufacturing process of the drug product.

PMDA accepted the applicant's explanation, based on the conclusion that the quality of the drug product to be marketed in Japan is ensured, for the following reasons: (a) these tests are included in the specifications for the drug substance, (b) the tests are carried out as part of the in-process control tests in the manufacturing process of the drug product and the product is controlled using the same acceptance criteria as used for the specifications for the drug product marketed in the US and Europe, and (c) it is confirmed by transportation validation that the drug product shipped from the manufacturer is stored and transported without loss of quality.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i). A Summary of the submitted data

The following primary pharmacodynamics studies were conducted: Effect on co-stimulatory signal of CD28, effect on T-cell proliferation and cytokine production, effect on T cell-dependent antibody production, effect on a collagen-induced arthritis model, effect on CTLA-4 expression, and effect on the defense mechanism against infection. No safety pharmacology studies were conducted. Instead, safety pharmacology core battery items were investigated based on the results of 1-month and 1-year intermittent intravenous toxicity studies in cynomolgus monkeys according to ICH Guidelines [see "3.(iii) Summary of toxicology studies"]. No secondary pharmacodynamics studies or pharmacodynamic drug-drug interaction studies have been conducted.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Effect on co-stimulatory signal of CD28

(a) Binding to CD80/CD86 and Fc receptor (4.2.1.1-13)

Binding ability of abatacept to CD80/CD86 and to the Fc receptor was investigated by flow cytometry, using the human B lymphoblastoma cell line Raji (expressing CD80 and CD86) and the macrophage-derived cell line U937 (expressing CD32 and CD64). Abatacept bound to U937 and Raji, whereas human IgG1 bound to U937, which demonstrated that abatacept bound to CD80/CD86 via the extracellular domain of CTLA-4 and to the Fc receptor via the Fc domain of human IgG1.

(b) Effect on complement-dependent cytotoxic activity (4.2.1.1-11)

The Epstein-Barr virus-transformed, CD80/CD86-positive human B lymphoblast cell line (PM-LCL) was cultured in the presence of abatacept, anti-CD80 antibody, or anti-CD86 antibody (0.001-10 μg/mL), followed by continued culture by adding complement. As a result, complement-dependent cytotoxicity was induced in the presence of anti-CD80 antibody or anti-CD86 antibody (positive controls) at concentrations of ≥0.01 μg/mL, whereas no cytotoxicity was induced by abatacept at any concentrations tested. The applicant explains that introduction of mutations in the hinge domain of IgG1 in abatacept had abolished the cytotoxic activity.

3.(i).A.(1).2) Effects on T cell proliferation and cytokine production

(a) Effects on the proliferation of naïve T cells and on cytokine production (4.2.1.1-1, 4.2.1.1-3)

The effect of abatacept (0-100 μg/mL) on CD28 co-stimulatory signal-mediated proliferation of human naïve T cells was investigated, using the mixed lymphocyte reaction (MLR) between human peripheral blood T cells and T cell-depleted human peripheral blood monocytes (E-PBMC) prepared, from different donors as the index. Abatacept significantly suppressed the proliferation of naïve T cells at concentrations of ≥3.16 μg/mL, but no further enhancement in the suppressing effect was observed at higher concentrations. When PM-LCL was used in place of E-PBMC, a significant suppression was observed at abatacept concentrations of ≥0.316 μg/mL and above, and the suppressing effect reached the maximum level at 10 μg/mL.

In a separate study, the effect of abatacept (0-100 μg/mL) on the proliferation of human naïve T cells was investigated, using the MLR between human peripheral blood T cells and PM-LCL as the index. Abatacept significantly suppressed the proliferation of T cells at concentrations of ≥0.3 μg/mL, showing the maximum effect at 3 μg/mL. In addition, the effect of abatacept (30 μg/mL) on cytokine production by T cells was investigated. Productions of IL-2, IFN-γ, and TNF-α were significantly suppressed from 24 up to 72 hours after stimulation.

(b) Effects on the proliferation of memory T cells and cytokine production (4.2.1.1-2, 4.2.1.1-3)

The effect of abatacept (0-100 μg/mL) on the proliferation of human memory T cells was investigated by stimulating human peripheral blood monocytes (PBMC) with tetanus toxin in the presence of abatacept. Abatacept significantly suppressed the proliferation of memory T cells at concentration of ≥0.41 μg/mL, at concentration of ≥1.23 μg/mL, no significant difference was observed in the suppressing effect as compared with that at 100 μg/mL.

The effect of abatacept (30 μg/mL) on the tetanus toxin-stimulated proliferation of human memory T cells was investigated, using the MLR between T cells prepared from human bone marrow cells and PBMC derived, from the same donor as the index. Abatacept suppressed the proliferation of human memory T cells by 60% to 80%. Also, the effect of abatacept (30 μg/mL) on cytokine production by T cells was investigated. Abatacept significantly suppressed the productions of IL-2 (at 24, 48, and 96 hours after stimulation), IFN-γ (at 48 and 96 hours after stimulation) and TNF-α (at 96 hours after stimulation).

Based on the results of these studies (4.2.1.1-1 to 3, 4.2.3.7.7-1 and 2), the applicant explains that the maximum clinical efficacy is expected to be achieved at ≥10 μg/mL concentration of abatacept.

(c) Effects on monocytes and macrophages (4.2.1.1-4, 4.2.1.1-14)

When human monocytes were stimulated with lipopolysaccharides (LPS) in the presence of abatacept (30 μg/mL), abatacept did not affect TNF-α production by monocytes. Also, human monocytes were cultured in the presence of abatacept (30 μg/mL) alone, or in the presence of abatacept (30 μg/mL) and an insoluble immune complex (complex of human IgG and goat anti-human IgG antibody). As a result, abatacept alone scarcely induced TNF-α production, and it did not affect immune complex induced TNF-α production.

3.(i).A.(1).3) Effects on T cell-dependent antibody production

(a) Effects on T cell-dependent antibody production (4.2.1.1-10)

After primary immunization of male and female cynomolgus monkeys (4 to 6 in each group) with mouse L6 monoclonal antibody, keyhole limpet hemocyanin (KLH), or bacteriophage φX174, abatacept (2 or 8 mg/kg) was administered intravenously twice weekly for 7 weeks and, at the end of administration, the secondary immunization with the same antigen was performed. Abatacept at both doses suppressed productions of the primary and secondary antibodies against mouse L6 antibody by ≥99% compared with the control group (IgG group). Production of the primary antibody against KLH was suppressed by 83% and 86% in the 2 and 8 mg/kg groups, respectively, whereas production of the secondary antibody was not suppressed in the 2 mg/kg group but was suppressed by 87% in the 8 mg/kg group. Abatacept suppressed productions of the primary and secondary antibodies against bacteriophage φX174 as well, but the effect was not statistically significant.

(b) Effect on immune tolerance induction (4.2.1.1-6)

After primary immunization (Day 1) of male and female cynomolgus monkeys (4 per group) with sheep red blood cells (SRBC), a T cell-dependent antigen, abatacept (1, 2.9, or 8.7 mg/kg) was administered intravenously on Days 1, 4, 8, 11, 15, and 18, production of the primary

antibody was suppressed dose-dependently by 71% to 98%. When the secondary immunization was performed on Day 102, the time when abatacept eliminated from the blood, production of the secondary antibody was suppressed by 33% to 81%.

The applicant considers immune tolerance to not have been induced, based on the finding that the amount of secondary antibody production at 8.7 mg/kg abatacept was comparable to the amount of primary antibody production in the control (0 mg/kg) group.

3.(i).A.(1).4) Effects on collagen-induced arthritis model (4.2.1.1-5)

The effects of prophylactic and therapeutic administration of abatacept on collagen-induced arthritis (CIA) model rats were investigated. Abatacept (1 mg/kg) was administered intraperitoneally to female CIA rats (8 per group) on Days -1, 0, 2, 4, 6, 8, and 10, with the day of collagen administration counted as Day 0. Pedal oedema was observed from Day 16 in the group treated with human IgG, whereas no pedal oedema was observed in the group treated with abatacept prophylactically, significantly suppressed even on and after Day 16. Also, these rats showed suppression of anti-collagen IgG antibody production, suppression of productions of cytokines such as IFN-γ, TNF-α, IL-1α, and IL-2, and a significant suppression of bone destruction. When abatacept (1 mg/kg) was administered intraperitoneally to female CIA rats (6 or 7 per group) on Days 10, 12, 14, 16, 18, and 20, delayed progression of pedal oedema was observed up to Day 19, whereas the oedema at the end of the study (Day 27) was comparable to that observed in the group treated with human IgG. No significant suppression of anti-collagen IgG antibody titer, cytokine (IL-2, IFN-γ, and TNF-α) productions, or bone destruction was observed.

3.(i).A.(1).5) Effect on CTLA-4 expression (4.2.1.1-12)

The effect of abatacept (30 μg/mL) on the expression of CTLA-4 on the surfaces of activated T cells was investigated, using the MLR between human peripheral blood T cells and PM-LCL as the index. Abatacept decreased the number of activated (CD25-positive) T cells but did not suppress the expression of CTLA-4 on the surfaces of CD25-positive T cells.

3.(i).A.(1).6) Effects on the defense mechanism against infection

(a) Effects on the defense mechanism against murine cytomegalovirus (CMV) infection (4.2.1.1-9)

Abatacept (200 μg/body) was intravenously administered to female mice (18 per group) twice weekly for 2 weeks, followed by an inoculation with murine cytomegalovirus (mCMV). Symptoms of infection were observed in 2 of 18 mice on Days 5 to 7 after mCMV inoculation, however, the symptoms resolved in all mice by Day 8. Viral titers in the liver and in the salivary glands significantly increased on Days 4 and 21, respectively, after mCMV inoculation as compared with the group treated with human IgG, but no viral titer increase was observed in the lungs or the spleen.

(b) Effect on the defense mechanism against *Pneumocystis carinii pneumonia* (4.2.1.1-9)

Abatacept (200 μg/body) was intravenously administered to 10 female mice twice weekly for 3 weeks before inoculation with *Pneumocystis carinii* and for 4 weeks after inoculation. As a result, no decrease in body weight, symptoms of infection, or death was observed, similar to the results in the untreated group (5 rats).

3.(i). B Outline of the review by PMDA

PMDA asked the applicant to discuss the reason for the failure of abatacept to exhibit efficacy in CIA rats when administered after the disease onset.

The applicant explained as follows:

It is considered that, in CIA rats, naïve T cells play an important role mainly in

immunosensitization (induction by collagen) and in the onset of the disease during its early stage, whereas memory/effector T cells are involved in the later stage of the disease. Since naïve T cells are more dependent on the CD28 co-stimulatory signal as compared with memory T cells, administration of abatacept at an early stage of the disease will likely achieve higher efficacy. Regarding the reasons for the failure of abatacept to exhibit efficacy when given after disease onset, there were possibly too many memory T cells or the disease might have been controlled not by T cells but rather by inflammatory cells, but no definite cause is known. The applicant also explained that there is a published report showing that administration of CTLA4Ig intraperitoneally to CIA mice after the onset of arthritis resulted in a significant decrease in clinical evaluation scores and a significant suppression of pedal oedema, demonstrating the therapeutic efficacy of CTLA4Ig (Webb LMC et al. *Eur J Immunol*. 1996;26: 2320-2328).

On the basis of the application data and the explanation of the applicant as above, PMDA concluded that the CD80/CD86 receptor-mediated pharmacological effect of abatacept has been demonstrated, and abatacept is thus expected to be effective for RA.

3.(ii) Summary of pharmacokinetic studies

3.(ii). A Summary of the submitted data

Pharmacokinetics of abatacept following intravenous or subcutaneous administration were investigated in mice, rats, rabbits, and monkeys.

Concentrations of abatacept in sera of mice, rats, rabbits, and monkeys and also in rat milk were measured by enzyme-linked immunosorbent assay (ELISA) using microtiter plates coated with anti-abatacept monoclonal antibody (clone 7F8) (lower limit of quantitation, 1.0-2.0 ng/mL in serum, 3.0 ng/mL in rat milk). Anti-abatacept antibody titers were measured by ELISA using microtiter plates coated with abatacept. Pharmacokinetic parameters are expressed as means or means ± standard deviation (SD), unless indicated otherwise.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single dose study (4.2.2.2-1 to 3, 4.2.2.7-1, 5, 6)

A single dose of abatacept was subcutaneously or intravenously administered to mice and rats or intravenously to rabbits and monkeys. As a result, the following pharmacokinetic parameters were obtained (Table 4).

Table 4. Pharmacokinetic parameters following a single dose administration of abatacept to mice, rats, rabbits, and monkeys

	Dose (mg/kg)	No. of animals	Route of administration	C_{max} (μg/mL)	T_{max} (h)	AUC (μg·h/mL)	Vss (L/kg)	CLT (mL/h/kg)	$t_{1/2}$ (day)	BA (%)
Mice	14[a]	8	s.c.	59	12	7153	-	-	3.2	85
	14[a]	8	i.v.	281	0.05	8384	0.19	1.8	3.8	-
	0.33[b]	6	i.v.	323	0.05	9490	3.4 mL	0.03 mL/h	2.8	-
	0.5[b]	6	s.c.	96	24	15,800	-	-	3.6	110
	1.6[b]	6	s.c.	315	12	45,200	-	-	5.2	98
	3.3[b]	6	s.c.	726	9	73,800	-	-	4.0	78
	3.6[c]	3	i.v.	56.8	-	1594	0.11	2.0	0.8	-
	14[c]	3	i.v.	290.3	-	8705	0.14	1.5	2.5	-
	29[c]	3	i.v.	563.4	-	15,322	0.16	2.0	2.9	-
Rats	10	6	s.c.	26	48 (24, 96)*	5536	-	-	3.1	62.5
	80	6	s.c.	133	48 (48, 48)*	35,153	-	-	5.5	55.7
	200	6	s.c.	263	36 (24, 48)*	56,900	-	-	7.0	41.1
	10	6	i.v.	243	0.05	8857	0.15	1.2	2.7	-
	80	6	i.v.	2162	0.05	63,167	0.19	1.3	4.5	-
	200	6	i.v.	4610	0.05	138,608	0.24	1.5	7.1	-
Rabbits	10	4	i.v.	289	0.05	5940	0.13	1.7	2.4	-
Monkeys	10	4	i.v.	372	-	13,829	0.14	0.7	5.0	-
	33	4	i.v.	1086	-	46,006	0.17	0.7	7.5	-

Mean; *, median (min, max); C_{max}, maximum serum concentration; T_{max}, time to maximum serum concentration; AUC, area under serum concentration-time curve; Vss, distribution volume under steady state; CLT, total body clearance; $t_{1/2}$, elimination half-life; BA, bioavailability

Only females were used in studies with mice and rabbits. Since rats and monkeys did not show any sex difference, combined data of male and female animals were subjected to evaluation.

Mice, a: 4.2.2.2-1, b: 4.2.2.2-2, c: 4.2.2.7-1; rats, 4.2.2.2-3; rabbits, 4.2.2.7-5; monkeys, 4.2.2.7-6

Both C_{max} and AUC_{inf} increased with dosage, but showed different dose-response correlations depending on the study. For all animal species, $t_{1/2}$ increased with dosage. Particularly in mice, $t_{1/2,}$ following intravenous administration of approximately 3.6 mg/kg of abatacept, was extremely small compared with that in higher dose groups. It has been shown that anti-abatacept antibody is produced when the serum abatacept concentration decreased to <1 μg/mL in a repeat dose study in mice (4.2.2.7-16). In the above study, the serum abatacept concentration was approximately 1 μg/mL, which therefore suggests, although the anti abatacept antibody was not measured, that the clearance of abatacept was increased by the antibody produced.

3.(ii).A.(1).2) Repeat-dose studies (4.2.2.2-3, 4.2.2.7-13, 14, 17, 18, 19)

Abatacept, 0.07 mg (approximately 3.6 mg/kg) and 0.29 mg (approximately 14 mg/kg), was intravenously administered to 36 female mice once every 2, 3, or 4 days for a total of 7 doses. As a result, $t_{1/2}$ after the last dose were 2.7, 2.5, and 1.9 days in the 0.07 mg group, respectively, being the shortest in rats receiving abatacept once every 4 days. In contrast, in the 0.29 mg group, $t_{1/2}$ were 5.7, 4.7, and 4.5 days, all being similar. The AUC_{inf} values in the higher dose groups were 7 to 13 fold greater than those in the lower dose groups, showing a more than dose-proportional increase, from which the applicant considers that the clearance was higher in the 0.07 mg group than in the 0.29 mg group, and that the difference was due to the production of anti-abatacept antibody. Pharmacokinetics with repeated administration were investigated in the repeat-dose toxicity study in mice etc. Results showed that the systemic exposure level after repeated administration once weekly for 26 weeks was approximately 1.5 to 2.0 fold of that observed on Week 1.

Abatacept (10 mg/kg) was subcutaneously or intravenously administered to rats (3 males and 3 females per group) once every 2 days for a total of 7 times. As a result, C_{max} after the last dose were 99.3 and 414.8 μg/mL, i.e. approximately 3.8 and 1.7 times of those observed on Day 1. $AUC_{0\text{-}t}$ following repeated administration were 4339.8 and 9411.5 μg hours/mL, respectively, which were approximately 4.7 and 3.1 times of those observed following single dose administration. $t_{1/2}$ were 4.0 and 4.8 days, respectively.

Abatacept (1.0, 2.9, 8.7 mg/kg) was intravenously administered to monkeys (2 males and 2 females per group) on Days 1, 4, 8, 11, 15, and 18. As a result, the serum abatacept level reached the steady state by Day 11, and C_{max} and AUC_{0-t} following the last dose increased almost in a dose proportional manner. $t_{1/2}$ was within the range of 3.8 to 6.7 days, regardless of the dose.

Abatacept (10, 22.4, 50 mg/kg) was intravenously administered to monkeys (3 males and 3 females per group) once every 2 days for a total of 15 doses. As a result, C_{max} and AUC_{0-t} increased almost in a dose proportional manner, and C_{max} after the last dose were approximately 1.9, 2.0, and 1.6 times of those observed on Day 1. $t_{1/2}$ in the 50 mg/kg group were approximately 2 and 6 times of those in the 22.4 and 10 mg/kg groups, respectively. Anti-abatacept antibody was detected in the 10 and 22.4 mg/kg groups, from which the applicant considers that this caused the increased elimination rate observed in these groups. $t_{1/2}$ before antibody production (within 43 days after the last dose) was within the range of 8.2 to 11.7 days, regardless of the dose.

Abatacept (10, 22, 50 mg/kg) was intravenously administered to monkeys (5 males and 5 females per group) once weekly for 52 weeks. As a result, C_{max} and AUC_{0-t} increased almost in a dose proportional manner. The values on Day 78 were 1.3 to 1.8 times of those observed on Day 1, 1.6 to 2.3 times on Day 267, and 1.8 to 3.1 times on Day 358. $t_{1/2}$ following the last dose was within the range of 4 to 9 days regardless of the dose.

3.(ii).A.(1).3) Single dose comparative study of drug products (4.2.2.7-7, 4.2.2.7-9, 4.2.2.7-11)

During the process of development, the manufacturing process of abatacept was changed. In order to evaluate the comparability of the pharmacokinetic profiles of the pre- and post- change product, a single dose study in monkeys was conducted.

The lyophilized formulation of abatacept manufactured by process A and the reconstituted solution used in non-clinical studies were intravenously administered in a single dose of 10 mg/kg to monkeys (2 males and 2 females per group). A statistically significant difference was observed in both treatment groups regarding Vss (155.5 ± 11.1 and 131.4 ± 14. 9 mL/kg, respectively), whereas no significant difference was observed in C_{max} (336.3 ± 77.3 and 333.9 ± 45.8 μg/mL) or in AUC_{inf} (13,173 ± 2217 and 16,902 ± 2868 μg hours/mL), from which the applicant has considered that the two formulations of abatacept have similar pharmacokinetics.

The process D formulation and the process E formulation (10 mg/kg) were intravenously administered in a single dose to female monkeys (6 per group). The mean (90% confidence interval [CI]) of ratios (process E/process D) of C_{max} and AUC_{0-t} were 1.02 (0.88, 1.18) and 1.20 (1.03, 1.38), respectively. Although AUC_{0-t} of the process E formulation was higher than that of the process D formulation, $t_{1/2}$, CL and Vss of these formulations had similar values (or) minimal discrepancies, from which the applicant considers that the observed difference in AUC_{0-t} was not biologically significant, and therefore that the pharmacokinetics are similar for abatacept manufactured by process D and that manufactured by process E. Decreased serum potassium concentration and increased BUN were observed in the process E formulation group. However, the applicant judges that they are not toxicologically significant because the observed serum potassium concentration was within the range of the historical data of the site and, as regards BUN, no increase in serum creatinine concentration was observed. From these results and reasoning, the applicant has considered that the two formulations have similar safety profiles.

The process E formulation and the process F formulation (10 mg/kg) were intravenously

administered in a single dose to monkeys (9 males and 9 females per group). The mean (90% confidence interval [CI]) for ratios (process F/process E) of C_{max} and AUC_{inf} were 1.05 (0.98, 1.14) and 0.94 (0.88, 0.99), respectively, from which the applicant has considered that abatacept manufactured by process E and that manufactured by process F are biologically equivalent to each other. No treatment-related changes were observed in animals, from which the applicant judges that the two formulations have similar safety profiles.

3.(ii).A.(2) Distribution

Abatacept, because of its protein nature, is assumed to be rapidly degraded in the body and reincorporated into other proteins and peptides for reuse, precluding interpretation of the results. Therefore, no tissue distribution studies using radioisotope-labeled abatacept were conducted. Pharmacokinetic studies in pregnant and lactating animals and studies on placental transfer were conducted using non-labeled abatacept.

3.(ii).A.(2).1) Pharmacokinetics in pregnant and lactating animals (4.2.2.7-20, 4.2.2.7-22)

Abatacept (45, 200 mg/kg) was intravenously administered to pregnant rats (16 per group) once daily from Gestational Day 6 to 15. C_{max} were 1279 and 4154 μg/mL and AUC_{tau} were 15,009 and 49,281 μg hours/mL, respectively, after the last dose. Abatacept (45, 200 mg/kg) was intravenously administered to lactating rats (16 per group) once every 3 days from Gestational Day 6 to 21 and from Lactation Day 3 to 12. C_{max} were 891 and 3870 μg/mL and AUC_{tau} were 14,983 and 54,646 μg hours/mL, respectively, after the last dose.

Abatacept (200 mg/kg) was intravenously administered to 5 pregnant rabbits once every 3 days from Gestational Day 7 to 19. C_{max} was 6330.4 μg/mL, T_{max} was 0.05 h, and AUC_{tau} was 145,680.6 μg hours/mL, after the last dose.

3.(ii).A.(2).2) Placental transfer (4.2.2.2-4, 4.2.2.7-21)

Abatacept (10, 45, 200 mg/kg) was intravenously administered to pregnant rats (10 per group) once daily from Gestational Day 6 to 15. Serum abatacept concentrations in dams on Gestational Day 20 were 8.4 ± 7.4, 26.7 ± 7.9, and 81.0 ± 38.9 μg/mL, respectively, and serum abatacept concentrations in fetuses were 5.0 ± 2.4, 14.7 ± 6.5, and 33.1 ± 7.4 μg/mL, respectively, showing that abatacept crosses the placenta. The ratios of the abatacept concentration in fetal serum to that in dam serum were 0.60, 0.55, and 0.41, respectively.

Abatacept (10, 45, 200 mg/kg) was intravenously administered to pregnant rabbits (5 per group) once every 3 days from Gestational Day 7 to 19. Serum abatacept concentrations in dams on Gestational Day 19 were 200.7 ± 27.8, 989.7 ± 162.7 and 7261.2 ± 3699.7 μg/mL, respectively, and serum abatacept concentrations in fetuses were 0.6 ± 0.7, 1.1 ± 0.7, and 4.3 ± 1.7 μg/mL, respectively. The ratios of the abatacept concentration in fetal serum to that in dam serum were less than 0.003, 0.001, and 0.001, respectively.

3.(ii).A.(3) Metabolism and excretion

Abatacept is assumed to be metabolized to amino acids via the same degradation pathway as that of endogenous and food-derived proteins. In addition, from a practical standpoint, it is difficult to interpret the results of excretion studies using radioisotope-labeled abatacept. Furthermore, non-metabolic excretion routes such as renal excretion and biliary excretion are unlikely to be involved in the excretion of most protein drug products. For these reasons, no studies on metabolism or excretion were conducted. A study on the excretion of abatacept into milk was, however, conducted.

3.(ii).A.(3).1) Excretion into milk (4.2.2.5-1)

Abatacept (10, 45, 200 mg/kg) was intravenously administered to pregnant rats (10 per group) roughly once every 3 days from Gestational Day 6 to Lactation Day 21. As a result, abatacept

was detected in the serum and milk of dams on Lactation Day 12, and the ratios of abatacept in the milk to that in the serum were 0.09 in the 10 mg/kg group, 0.09 in the 45 mg/kg group, and 0.08 in the 200 mg/kg group. Abatacept concentrations in the serum and milk of dams increased almost in a dose proportional manner. Abatacept was detected in the serum of F1 rats on Postpartum Day 21 as well.

3.(ii).B Outline of the review by PMDA

As a reason for not conducting excretion studies on abatacept, the applicant explained that non-metabolic routes such as renal excretion are not involved in the excretion of most protein drug products. However, a relationship between the abatacept exposure level and the glomerular filtration rate (GFR) is suggested by the population pharmacokinetic (PPK) analysis of Japanese RA patients investigated in a clinical study. PMDA therefore asked the applicant to further discuss the effect of the kidney on the excretion of abatacept, based on these findings as well.

The applicant explained as follows:
It is suggested that the kidney plays an important role in excretion of biological products with relatively small molecular weights (M.W. 17.3 kD), such as anakinra (IL-1 inhibitor, unapproved in Japan) (Yang BB et al. *Clin Pharm Thera.* 2003;74: 85-94). For the excretion of protein drug products with a large molecular weight, such as abatacept (M.W. ca. 100 kD), in contrast, the kidney is unlikely to be involved. On the other hand, it is reported that some protein drug products are eliminated via receptor-mediated uptake and intracellular metabolism (Tang L et al. *J Pharm Sci.* 2004;93: 2184-2204). In light of these findings, abatacept also appears to undergo renal metabolism, albeit to an unknown extent. However, even if the renal metabolism of abatacept is affected by impaired renal function, the drug is assumed to be excreted via other routes such as protein-degrading enzymes ubiquitous in the body and endocytosis by hepatocytes. Therefore, abatacept is unlikely to accumulate in the body in patients with impaired renal function. Regarding the results of clinical studies, although the PPK analysis in Japanese RA patients showed a tendency for a decrease in the estimated clearance value with a decrease in GFR, no similar trend was observed in the PPK analysis in non-Japanese RA patients. Based on the estimated exposure level in Japanese patients being within the range of the estimated exposure level in non-Japanese patients, abatacept exposure is unlikely to increase to a clinically significant level in patients within a GFR range of 35 to 118 mL/min/1.73m^2 (including mild to moderate renal impairment), which was the range observed in Japanese patients enrolled in the clinical study.

PMDA accepts the explanation of the applicant, but considers that it is necessary to further investigate the relationship between renal function and the safety of abatacept in the post-marketing surveillance since RA patients often have the complication of a renal disorder, including adverse drug reactions due to anti-rheumatic agents, and abatacept is therefore expected to be administered to patients with more advanced renal impairment in the clinical setting.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The following toxicology studies were conducted on abatacept: single dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, toxicity studies in neonates, local tolerance studies, and other toxicity studies (immunotoxicity studies, studies on the mechanism of toxicity, toxicity studies on impurities). Some of the other toxicity studies were conducted under non-GLP conditions, and were therefore evaluated as reference data.

Anti-abatacept antibody was produced in all animals used in toxicity studies, but the antibody

was detected only during the recovery period in most of the cases. The exposure level of abatacept was therefore confirmed to have been maintained during the treatment period in all studies.

3.(iii).A.(1) Single dose toxicity (4.2.3.1-2, 4.2.3.2-1 to 2)

A single dose toxicity study in cynomolgus monkeys was conducted in which abatacept (0, 10, 33, 100 mg/kg) was intravenously administered. No death or changes in clinical symptoms were observed, from which the approximate lethal dose was estimated to be ≥100 mg/kg. No single dose toxicity study in rodents was conducted. Instead, the single dose toxicity was evaluated in a 6-month intermittent subcutaneous administration study in mice (4.2.3.2-1) and a 2-week intermittent subcutaneous/intravenous administration study in rats (4.2.3.2-2). There were no signs of acute toxicity after the initial dose of 200 mg/kg, the maximum dose tested, in either study.

3.(iii).A.(2) Repeat-dose toxicity

For repeatdose toxicity studies, a subcutaneous administration study in mice (6 months), subcutaneous and intravenous administration studies in rats (2 weeks), and intravenous administration studies in cynomolgus monkeys (1 month, 1 year) were conducted. All studies showed a decreased serum IgG level which was considered to be due to the pharmacological action of abatacept. Increased incidences of chronic multifocal inflammation in the kidney and of giant nuclei accompanied by degeneration of tubular epithelial cells were observed in mice. The ratio of the no adverse effect level (NOAEL) (mice, 200 mg/kg; cynomolgus monkeys, 50 mg/kg) in mice (6 months) and cynomolgus monkeys (1 year) to the exposure level (AUC) in humans treated with the clinical dose (10 mg/kg) for 1 month was estimated to be 4.7 times in mice and 9.5 times in monkeys. In the 3-month intermittent intravenous immunotoxicity study in rats (4.2.3.2-6), toxicity on the immune system was mainly evaluated. Therefore, the results were evaluated as toxicity in "other toxicity studies".

3.(iii).A.(2).1) Six-month intermittent subcutaneous administration study in mice (4.2.3.2-1)

Abatacept was subcutaneously administered at the dose levels of 0 (vehicle comprising 4% maltose, 10 mM sodium phosphate, 20 mM sodium chloride), 20, 65, and 200 mg/kg to male and female mice once weekly for 6 months. As a result, a decreased B cell ratio in the spleen, a transient decrease in serum IgG, and suppression of blastogenic responses of B and T cells were observed in mice treated with ≥65 mg/kg doses of abatacept, and these effects were considered to be due to the pharmacological action of abatacept. Increased incidences of mild chronic multifocal inflammation in the kidneys and of giant nuclei accompanied by degeneration of tubular epithelial cells were observed at ≥65 mg/kg. However, the applicant considers the kidney findings to be of low toxicological significance, for the following reasons: (i) no histopathological changes suggestive of effects on renal function or of renal disorder were observed, (ii) giant nuclei in the tubular epithelial cells and chronic multifocal inflammation resolved after a withdrawal period of 4 months, and (iii) the giant nuclei were due to the progression of age-related changes, as analyzed by electron microscopy. Other findings were increased spleen weight and decreased thymus weight at ≥65 mg/kg, but no histopathological abnormalities were observed. Administration of abatacept did not affect the expression of the cell proliferation marker Ki67 antigen in mammary tissue, from which the applicant considers early signs of carcinogenicity to be absent. The NOAEL was estimated to be 200 mg/kg.

3.(iii).A.(2).2) Two-week intermittent subcutaneous/intravenous administration study in rats (4.2.3.2-2)

Abatacept was subcutaneously administered at the dose levels of 0 (vehicle comprising 20% maltose, 100 mM sodium phosphate, 200 mM sodium chloride), 80, and 200 mg/kg, or intravenously at the dose levels of 0 (vehicle comprising 5% maltose, 25 mM sodium phosphate,

50 mM sodium chloride) and 200 mg/kg, to male and female rats once every 2 days for 2 weeks. Following both administrations, decreased levels of serum IgG and IgA were observed, and they were considered to be due to the pharmacological action of abatacept. No other treatment-related changes were observed, from which the NOAEL was estimated to be 200 mg/kg.

3.(iii).A.(2).3) One-month intermittent intravenous administration study in monkeys (4.2.3.2-3)

Abatacept was intravenously administered at the dose levels of 0 (vehicle comprising 25 mM sodium phosphate, 50 mM sodium chloride), 10, 22.4, and 50 mg/kg to male and female cynomolgus monkeys once every 2 days for 1 month. A serum IgG level decrease, attributable to the pharmacological action of abatacept, was observed at ≥10 mg/kg, and tended to show recovery after withdrawal of the drug. No other treatment-related changes were observed. Safety pharmacology-related effects, such as those on cardiovascular, neurological, and respiratory systems, were not observed. The NOAEL was estimated to be 50 mg/kg.

3.(iii).A.(2).4) One-year intermittent intravenous administration study in monkeys (4.2.3.2-5)

Abatacept was intravenously administered at the dose levels of 0 (saline), 10, 22, and 50 mg/kg to male and female cynomolgus monkeys once weekly for 52 weeks. A transient decrease in serum IgG was observed at 50 mg/kg, and atrophies of the spleen and the mandibular lymph node reflecting decreased activity in the germinal center were observed in males and females of all dose groups. These changes are considered to be related to the pharmacological action of abatacept. After withdrawal of abatacept for 13 weeks, KLH-induced antibody production was confirmed in all dose groups, coupled with a tendency for recovery in the histopathological changes in the spleen and in the mandibular lymph node. In the viral test performed before administration of abatacept, viral infection (simian herpes virus [herpes virus B], rhesus cytomegalovirus [RhCMV], simian papovavirus [SV40], or rhesus lymphocryptovirus [RhLCV]) was detected in all animals, but no virus-induced clinical signs following the administration of abatacept were noted. No treatment-induced effects on the cardiovascular, neurological, or respiratory systems were observed. The NOAEL was estimated to be 50 mg/kg.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-1 to 3)

For *in vitro* genotoxicity studies, a bacterial reverse mutation study, a genetic mutation test in Chinese hamster ovary cells, and a chromosomal aberration test using human lymphocytes were conducted. All tests were negative. No *in vivo* genotoxicity tests were conducted.

3.(iii).A.(4) Carcinogenicity

Because of the concern about an increase in the incidence of tumor development induced by the immunosuppressive effect of abatacept, a carcinogenicity test was conducted using CD-1 mice. The incidence of lymphoma was increased at ≥20 mg/kg (0.8 times the exposure level in humans) and the incidence of mammary adenocarcinoma was increased in female mice treated with ≥65 mg/kg (1.9 times the exposure level in humans). The non-carcinogenic level was not estimated.

3.(iii).A.(4).1) Carcinogenicity test in mice (4.2.3.4.1-1)

Abatacept was subcutaneously administered at the dose levels of 0 (saline), 0 (vehicle comprising 4% maltose, 10 mM sodium phosphate, 20 mM sodium chloride), 20, 65, and 200 mg/kg to male and female CD-1 mice once weekly for 84 weeks (males) or 88 weeks (females). The incidence of lymphoma was increased at ≥20 mg/kg (1 of 60 males, 1 of 60 males, 18 of 60 males, 22 of 60 males, and 17 of 60 males, respectively, and 4 of 60 females, 7 of 60 females, 27 of 60 females, 35 of 60 females, and 34 of 60 females, respectively [in the order of saline, vehicle, 20 mg/kg , 65 mg/kg, and 200 mg/kg, same hereafter]), and the incidence of mammary

adenocarcinoma was increased in females of ≥65 mg/kg dose groups (1 of 60 females, 4 of 57 females, 1 of 55 females, 6 of 58 females, and 8 of 58 females). An increased incidence of haemangioma was observed at 200 mg/kg in males (0 of 60 males, 0 of 60 males, 0 of 60 males, 1 of 60 males, and 3 of 60 males). Haemangioma is a tumor often observed in mice, and the incidence was within the normal range of the historical data of the test site and similar to that in females in the vehicle group of the same study (3 of 60 females). Therefore, the applicant considered that haemangioma was not caused by abatacept. As a non-neoplastic lesion, the incidence of megakaryocytes in the tubular epithelium was increased at ≥20 mg/kg.

Viral test was performed to investigate the mechanism of the onset of lymphoma and mammary adenoma. Endogenous murine leukemia virus (MLV) DNA was detected in the genome of CD-1 mice, and murine mammary tumor virus (MMTV) was detected by immunohistochemical test and by electron microscopy. On the basis of the published reports (Maita K et al. *Toxicol Pathol*. 1988;16: 340-349, Krueger GRF. *Hematopoietic system*. Springer-Verlag; 1990:264-275, Medina D. *Methods in Cancer Research*. Academic Press; 1973: 3-53, Medina D. *The mouse in biomedical research*, 4. Academic Press; 1982:373-396.), the applicant considers that the treatment-induced increase in the incidences of lymphoma and mammary adenoma are related to the compromised immune surveillance against MLV and MMTV caused by the long-term immunosuppressive effect of abatacept.

3.(iii).A.(5) Reproductive and developmental toxicity

For reproductive and developmental studies, a study on fertility and early embryonic development to implantation in rats, studies of the effect on embryo-fetal development in mice, rats, and rabbits, and a study of effects on pre- and post-natal development, including maternal function in rats were conducted. No treatment-induced teratogenicity was observed in any of these studies, whereas an increased incidence of skeletal anomalies was observed in fetuses, and enhanced T cell-dependent antibody production and chronic diffuse thyroiditis in the F_1 offspring. Also, placental transfer of abatacept in rats and rabbits (4.2.2.2-4, 4.2.2.7-21) and excretion of the drug into milk in rats (4.2.2.5-1) were demonstrated [see "3.(ii) Summary of pharmacokinetics studies"].

3.(iii).A.(5).1) Studies on fertility and early embryonic development to implantation in rats (4.2.3.5.1-1)

Abatacept was intravenously administered once every 3 days at the dose levels of 0 (vehicle comprising 5% dextrose), 10, 45, and 200 mg/kg to male rats from 2 weeks before mating up to necropsy (after the end of cesarean section of females) and to female rats from 2 weeks before mating up to Gestational Day 7. No effects of abatacept were observed on clinical symptoms, body weight, food consumption, copulating capacity or fertility, or on early embryonic development. The NOAEL of abatacept was estimated to be 200 mg/kg (11 times the exposure level in humans) both for general and reproductive toxicity in dams and for developmental toxicity in embryos and fetuses.

3.(iii).A.(5).2) Embryo-fetal development

(a) Study in mice (4.2.3.5.2-1)

Abatacept was intravenously administered at the dose levels of 0 (vehicle comprising physiological saline), 10, 55, and 300 mg/kg to pregnant mice once daily from Gestational Day 6 to 15. No effect of abatacept was observed in dams. In fetuses, renal haemorrhage was observed (0 of 95 mice at 0 mg/kg, 2 of 125 mice at 10 mg/kg, 1 of 137 mice at 55 mg/kg, and 1 of 124 mice at 300 mg/kg), but was not dose-dependent and was observed only unilaterally, from which the applicant considers the observed renal haemorrhage to not have been caused by abatacept. No teratogenicity was observed in any of the treatment groups. The NOAEL of abatacept was estimated to be 300 mg/kg both for general and reproductive toxicity in dams and for developmental toxicity in fetuses.

(b) Study in rats (4.2.3.5.2-2)

Abatacept was intravenously administered at the dose levels of 0 (vehicle comprising 5% dextrose), 10, 45, and 200 mg/kg to pregnant rats once daily from Gestational Day 6 to 15. No effect of abatacept was observed in dams. In fetuses, increased incidences of skeletal anomalies (non-uniform ossification of parietal bone at ≥10 mg/kg, insufficient ossification of cervical arch at ≥45 mg/kg) were observed, but both were within the ranges of the historical data of the testing site and it is reported that these skeletal anomalies are caused by developmental delay (Carney EW & Kimmel CA. *Birth Defects Research (Part B)*. 2007;80: 473-496.), from which the applicant considers that they are of low toxicological significance. No teratogenicity was observed in any of the treatment groups. The NOAEL of abatacept was estimated to be 200 mg/kg (30 times the exposure level in humans) both for general and reproductive toxicity in dams and for developmental toxicity in fetuses.

(c) Study in rabbits (4.2.3.5.2-4)

Abatacept was intravenously administered at the dose levels of 0 (vehicle comprising physiological saline), 10, 45, and 200 mg/kg to pregnant rabbits once every 3 days from Gestational Day 7 to 19. As a result, no effect of abatacept was observed in either dams or fetuses. The NOAEL of abatacept was estimated to be 200 mg/kg (29 times the exposure level in humans) both for general and reproductive toxicity in dams and for developmental toxicity in fetuses.

3.(iii).A.(5).3) Study of effects on pre- and post-natal development, including maternal function in rats (4.2.3.5.3-1)

Abatacept was intravenously administered at the dose levels of 0 (vehicle comprising 5% dextrose), 10, 45, and 200 mg/kg to pregnant rats roughly once every 3 days from Gestational Day 6 to Postpartum Day 21. No effect of abatacept on dams was observed. In the F_1 offspring, enhanced production of T cell-dependent antibody against KLH was observed in females of the 200 mg/kg group. One of 10 neonates of the same group had chronic diffuse thyroiditis which was caused by severe infiltration of mainly lymphocytes and plasma cells, suggesting chronic lymphoplasmacytic thyroiditis. Therefore, the applicant considered that the disease was caused by autoimmunity. The NOAEL was estimated to be 200 mg/kg (11 times the exposure level in humans) for general and reproductive toxicity in dams and for the F_1 offspring (males), and 45 mg/kg (3 times the exposure level in humans) for the F_1 offspring (females).

During the review process, PMDA instructed the applicant to provide cautions in the package insert about the observations that abatacept crossed the placenta in rats and rabbits and that autoimmunity-like findings were noted in neonates in a study of effects on pre- and post-natal development in rats.

3.(iii).A.(5).4) Studies in juveniles

(a) Three-month subcutaneous/intravenous administration study in juvenile rats (4.2.3.5.4-1)

Abatacept was subcutaneously or intravenously administered (subcutaneously from Postnatal Day 4 to 28, intravenously from Postnatal Day 31 to 94) at the dose levels of 0 (vehicle comprising physiological saline), 20, 65, and 200 mg/kg once every 3 days to male and female juvenile rats of Postnatal Day 4. Death or a moribund condition was observed on Postnatal Day 34 to 161 (0 of 107 rats at 0 mg/kg, 10 of 194 rats at 20 mg/kg, 5 of 194 rats at 65 mg/kg, 12 of 194 rats at 200 mg/kg). Most of the rats that died or became moribund showed changes in general symptoms (e.g., decreased body weight, hunchback position, loose/liquid stools, dyspnea) and, from these findings and based on the microbiological test, the applicant judges that bacterial infection caused by the immunosuppressive effect of abatacept was associated

with the death and the moribund condition. At ≥20 mg/kg, changes in immunological parameters (e.g., decreased serum IgG, reduced response of T cell-dependent antibody against KLH, decreased regulatory T cell count, increased helper T cell count) were observed together with expansion of the T cell zone and shrinkage of the B cell zone in the spleen and lymph nodes. Other observations in rats of ≥20 mg/kg dose groups were increased incidences of lymphocytic infiltration in the thyroid and pancreatic islets, inflammation and mononuclear cell infiltration in the Harderian gland and the prostate gland. After a withdrawal period of 3 months, immunological parameters and histological changes in lymphatic organs tended to resolve, but lymphocytic infiltration in the pancreatic islets and in the thyroid and inflammation and mononuclear cell infiltration in the Harderian gland and the prostate gland did not show any tendency to resolve; instead, inflammation and mononuclear cell infiltration in the seminal vesicle were newly observed. The applicant considers that the lymphocytic infiltration in the thyroid and in the pancreatic islets has been caused by autoimmune reactions, judging from the histopathological characteristics. The inflammation and mononuclear cell infiltration in the Harderian gland, the prostate gland, and the seminal vesicle were qualitatively similar to those observed in the control group, from which the applicant considers that inflammatory and infiltrative responses observed even in the normal state were exacerbated by the immunosuppressive effect of abatacept. The NOAEL was estimated to be <20 mg/kg.

(b) Three-month subcutaneous/intravenous immunotoxicity study in juvenile rats (4.2.3.5.4-2)

In order to investigate whether or not the effect on the immune system observed in the 3-month subcutaneous/intravenous administration study in juvenile rats (4.2.3.5.4-1) was related to the treatment initiation on Postnatal Day 4 when the immune system was still underdeveloped, the study was repeated in a site that was maintained under a stricter microbiological control.

Abatacept (0 mg/kg [vehicle comprising saline] or 65 mg/kg) was subcutaneously or intravenously administered to male and female juvenile rats from Postnatal Day 4 once every 3 days (subcutaneously from Postnatal Day 4 to 28, intravenously from Postnatal Day 31 to 97) or abatacept (20 and 65 mg/kg) was subcutaneously or intravenously administered from Postnatal Day 28 once every 3 days (subcutaneously on Postnatal Day 28, intravenously from Postnatal Day 31 to 97). Skin symptoms (e.g., rash, inflammation) were observed in the tail at 65 mg/kg regardless of the age of treatment initiation (Postnatal Day 4 or 28), and 1 out of 10 rats in each group was sacrificed in a moribund state because of aggravation of the tail lesion. The applicant considers that the tail lesion was due to opportunistic infection caused by the immunosuppressive effect of abatacept. Regardless of the age at treatment initiation (Postnatal Day 4 or 28), changes in immunological parameters and histopathology, similar to those observed in the 3-month subcutaneous/intravenous administration study in juvenile rats (4.2.3.5.4-1), were observed. The NOAEL was estimated to be <20 mg/kg.

3.(iii).A.(6) Local tolerance

3.(iii).A.(6).1) Single dose, intravenous, intra-arterial, and perivenous irritation studies in rabbits (4.2.3.6-5)

A single dose of abatacept was administered to female rabbits intravenously (5 mg/animal), intra-arterially (5 mg/animal), or perivenously (2 mg/animal) to evaluate local irritating activity. No toxicologically significant findings were observed in intravenous or intra-arterial administration as compared with the control (saline) group, whereas very mild local irritation was observed with perivenous administration.

3.(iii).A.(7) Other toxicity studies

Immunotoxicity studies, studies on the mechanism of toxicity, toxicity studies on impurities, etc., were conducted.

3.(iii).A.(7).1) Immunotoxicity

The 3-month subcutaneous/intravenous immunotoxicity study in juvenile rats (4.2.3.5.4-1 to 2) showed effects on the immune system (e.g., decreased regulatory T cell count, increased helper T cell count, expansion of the T cell zone in lymphatic organs) and autoimmune-like inflammation (lymphocytic infiltration in the thyroid gland and pancreatic islets). Therefore, an immunotoxicity study was conducted in mature rats, which showed similar results to those observed in juvenile rats. Also, a study was conducted using model mice chronically infected with *Mycobacterium tuberculosis*. The applicant considers that defensive capacity of the host against the bacteria is not impaired by abatacept.

(a) Three-month intermittent-dose intravenous immunotoxicity study in rats (4.2.3.2-6)

Abatacept was intravenously administered to male and female rats at the dose levels of 0 (saline), 65, and 200 mg/kg once every 3 days for 3 months. Rats in the ≥65 mg/kg dose groups showed decreased serum IgG, increased helper T cell count, decreased regulatory T cell count, expansion of the T cell zone in the spleen and lymph nodes, lymphocytic inflammation in the thyroid gland and pancreatic islets, etc.

(b) Study on infection reactivation in model mice chronically infected with *Mycobacterium tuberculosis* (4.2.3.7.2-3)

Female C57BL/6 mice with chronic granulomatous infection by *Mycobacterium tuberculosis* were treated with abatacept (0.5 mg/animal) subcutaneously once weekly for 16 weeks or with anti-TNF-α (MP6-XT22) antibody (positive control, 0.5 mg/animal) intraperitoneally twice weekly. In the anti-TNF-α (MP6-XT22) antibody group, all mice had died by Week 9. They showed decreased body weight, increased *Mycobacterium tuberculosis* counts in the lungs, lymph nodes, and spleen, enhanced IFN-γ production by T cells in the lungs and lymph nodes, increased mononuclear cell infiltration in the lungs and spleen, and an increased number of granulomas. In contrast, mice in the abatacept group survived up to study completion (16 weeks), without showing effects on body weight, *Mycobacterium tuberculosis* counts, IFN-γ production, or histopathological findings.

3.(iii).A.(7).2) Study on the mechanism of toxicity (4.2.3.7.3-2)

In order to elucidate the relationship between MMTV and the increased incidence of mammary adenoma observed in the carcinogenicity study in mice (4.2.3.4.1-1), a study was conducted in which saline or abatacept (200 mg/kg) was subcutaneously administered once weekly for 26 weeks to female CD-1 mice that had been infected with MMTV. *In vivo* bioassay showed that MMTV infection increased the titer of IgG2a, an antibody subtype considered to be important for resistance against MMTV (Purdy A et al. *J Exp Med*. 2003;197: 233-243.), and induced neutralizing antibodies to an extent sufficient for suppressing MMTV infection. Subsequent administration of abatacept caused a slight suppression of the antibody response to MMTV. *In situ* hybridization and 5-bromo-2'-deoxyuridine (BrdU)-staining showed no evidence of viral or cellular proliferation, or of tumorigenesis. The applicant considers that the duration of treatment with abatacept was too short to evaluate tumorigenesis and that the antibody response to MMTV was not sufficiently suppressed under the experimental conditions used.

3.(iii).A.(7).3) Toxicity studies on impurities (4.2.3.7.6-1 to 3)

Single dose intravenous toxicity studies were conducted in mice and cynomolgus monkeys to evaluate the safety of impurities contained in process A or B drug substances and of aggregates that form when abatacept is dissolved/stored in silicon-coated syringes. No toxicologically significant changes were observed in either study.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Autoimmune-like findings

PMDA asked the applicant to discuss whether the autoimmune-like findings observed in the 3-month subcutaneous/intravenous immunotoxicity study in juvenile rats and in the 3-month intermittent intravenous immunotoxicity study in rats can be extrapolated to humans.

The applicant explained as follows:
The cause of the autoimmune-like findings observed in rats is unclear. However, judging from the lymphocytic infiltration in the thyroid gland and in the pancreatic islets accompanied by the decreased regulatory T cell count, the onset of autoimmune disease in rats appears to be associated with the decreased regulatory T cell count. In mice, on the other hand, despite the report claiming the decreased regulatory T cell count after 6 days of abatacept administration (Tang AL et al. *J Immunol.* 2008;181:1806-1813.), no signs suggestive of autoimmune disease were observed in either the 6-month intermittent-dose subcutaneous administration study or the 20-month carcinogenicity study. In addition, in cynomolgus monkeys, no signs suggestive of autoimmune disease were observed in the long-term repeated administration for up to 1 year although effects on regulatory T cells were not evaluated. These results raise the possibility that the findings observed in rats may have been due to species-specific sensitivity to abatacept. In the foreign pivotal clinical studies (IM101-100, 101, 102, 029, 031), the incidence of autoimmune-related adverse events was higher in the abatacept group (1.4% [28 of 1955 subjects]) than the placebo group (0.8% [8 of 989 subjects]), but most were events commonly observed in RA patients. The data accumulated from foreign clinical studies (5.3.5.3-7.2, 5.3.5.3-7.3) showed that the incidence of autoimmune disease-related adverse events have no tendency to increase depending on the duration of exposure (up to 8 years). Taking these facts into account, clinical use of abatacept is unlikely to increase the risk of autoimmune disease.

3.(iii).B.(2) Carcinogenicity
PMDA asked the applicant to explain whether the data for increased incidences of mammary adenoma and lymphoma associated with abatacept in the carcinogenicity study can be extrapolated to humans.

The applicant explained as follows:
In the carcinogenicity study in mice, it appears that the incidences of MLV- and MMTV-induced tumors increased because of the decreased immune surveillance, i.e. the pharmacological action of abatacept. However, given that humans have no viruses corresponding to MLV and that the human mammary tumor virus (HMTV) reportedly corresponding to MMTV is not an endogenous retrovirus (Mant C & Cason J. *Rev Med Virol*, 2004; 14: 169-177.), MLV- and MMTV-induced tumors are considered to be unique to mice and have no relation to humans. On the other hand, it is reported that tumor virus is reactivated in immunocompromised RA patients as a result of decreased immune surveillance (Park HB et al. *J Rheumatol*. 2004; 31: 2151-2155, Feng W et al. *J Nat Cancer Institute*. 2004; 96: 1691-1702). Therefore, malignant tumors caused by viruses are a potential safety risk in patients treated with drugs with immunoregulatory effects, such as abatacept. However, in the 1-year intermittent-dose intravenous study in cynomolgus monkeys, an animal species thought to be more appropriate than mice for evaluating the risk of tumor virus activation in humans, no neoplastic lesions or precancerous lesions were observed despite the presence of some animals that had been infected by a tumor virus, RhLCV, before treatment start. In addition, at present, no increase in the incidence of malignant tumors has been observed in Japanese or foreign clinical studies, or in foreign post-marketing data although the number of patients treated with abatacept and the evaluation period are still insufficient. These results suggest that abatacept is unlikely to increase the tumor incidence in humans.

3.(iii).B.(3) Nephrotoxicity
PMDA asked the applicant to explain whether the data from the repeat-dose toxicity and carcinogenicity studies in mice can be extrapolated to humans, despite the fact that giant nuclei

in tubular epithelial cells were observed in those studies.

The applicant explained as follows:
Some nephrotoxic or oncogenic substances are known to be associated with giant nuclei in tubular epithelial cells observed in rodents (Richardson JA & Woodard JC. *ILSI Monograph on Pathology Animals, Urinary System*. Springer-Verlag: 1986; 189-192). However, results of the 6-month intermittent-dose subcutaneous study and the carcinogenicity study in mice showed no effect of abatacept on renal function or histopathological changes suggestive of renal disorder such as loss of nephrons or tumor formation. Also, no similar findings were observed in the toxicity studies in which abatacept was administered to rats for up to 3 months or to cynomolgus monkeys for up to 1 year. These results suggest that the findings observed in mice treated with abatacept are of low toxicological significance. In addition, no noteworthy changes in creatinine levels were observed in Japanese and foreign clinical studies. Furthermore, the data accumulated from foreign clinical studies show that the incidence of renal and urological disorders during the double-blind period is similar between abatacept and placebo groups. These results suggest that the findings observed in mice are unlikely to occur in humans.

PMDA accepts the above explanation in general from the aspect of toxicology, but considers that, given the pharmacological action of abatacept, the possibility of the onset of autoimmune disease and the risk of carcinogenicity cannot be excluded and that safety in clinical use should be carefully investigated based on the results of the clinical studies, post-marketing surveillance data, etc.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and related analytical methods

4.(i).A Summary of the submitted data

Data of 2 foreign clinical studies in healthy adults (5.3.1.2-1, IM101-017; 5.3.1.2-2, IM101-065) were submitted as the evaluation data related to bioequivalence.

Abatacept concentrations in human serum were measured by ELISA using plates coated with anti-abatacept monoclonal antibody (clone 7F8) (lower limit of quantitation, 1 ng/mL) and by electrochemiluminescence immunoassay (lower limit of quantitation, 1 μg/mL). Cross validation of the ELISA assay and the electrochemiluminescence immunoassay has been performed as well.

4.(i).A.(1) Bioequivalence studies

4.(i).A.(1).1) Bioequivalence study between process D drug product and process E drug product (Study IM101-017, 5.3.1.2-1 [20 to 20])

In order to examine bioequivalence between the process D formulation and the process E formulation, a randomized, parallel group, comparative study was conducted in healthy non-Japanese adult subjects (15 subjects in process D group, 13 subjects in process E group).

A single dose of process D or process E formulation was administered by intravenous infusion at 10 mg/kg. The mean (90% CI) of ratios (process E/process D) of C_{max}, AUC_{0-t}, and AUC_{inf} of serum abatacept concentration were 1.05 (0.93, 1.18), 1.02 (0.90, 1.14), and 1.02 (0.90, 1.15), respectively, from which the applicant determines that the pre-change and post-change products are biologically equivalent.

Adverse events (except abnormal laboratory changes) were observed in 46.7% (7 of 15 subjects) in the process D group and in 80.0% (12 of 15 subjects) in the process E group. Events that occurred in at least 2 subjects in either of the groups were headache (2 subjects in group D, 5

subjects in group E) and nasopharyngitis (1 subject in group D, 2 subjects in group E). No deaths occurred. Serious adverse events were observed in 2 subjects of the process E group (duodenal ulcer perforation, upper limb fracture), and the causal relationship with the investigational product was not ruled out for duodenal ulcer perforation. There were no adverse events leading to treatment discontinuation. An abnormal laboratory change was observed in 1 subject of the process D group (white blood cells urine positive); the causal relationship of the abnormality with the investigational product was not ruled out.

4.(i).A.(1).2) Bioequivalence study between process E drug product and process F drug product (Study IM101-065, 5.3.1.2-2 [20 to 20])

In order to examine bioequivalence between the process E drug product and the process F drug product, a randomized, parallel group, comparative study was conducted in healthy non-Japanese adult subjects (17 subjects in process E group, 20 subjects in process F group).

A single dose of process E or process F drug product was administered by intravenous infusion at 10 mg/kg. The mean (90% CI) of ratios (process F/process E) of C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} of serum abatacept concentration were 0.992 (0.891, 1.104), 1.175 (1.053, 1.312), and 1.177 (1.043, 1.329), respectively. In the process F group, AUC_{inf} in 1 subject (70,161 μg·h/mL) was >90% higher than the median of the other subjects (36,710 μg·h/mL). When this subject was excluded from the calculation, the mean (90% CI) of ratios of C_{max}, $AUC_{0\text{-}t}$, and AUC_{inf} were 0.974 (0.878, 1.082), 1.145 (1.034, 1.267), and 1.141 (1.023, 1.273), respectively.

Adverse events (except abnormal laboratory changes) were observed in 78.9% (15 of 19 subjects) in the process E group and in 65.0% (13 of 20 subjects) in the process F group. The most common abnormal adverse events were nausea (0 in group E, 4 subjects in group F), nasopharyngitis (4 subjects in group E, 3 subjects in group F), headache (6 subjects each in groups E and F), and pharyngolaryngeal pain (4 subjects in group E, 1 subject in group F). No deaths occurred. A serious adverse event was observed in 1 subject of the process E group (osteomyelitis), for which a causal relationship with the investigational product was not ruled out. There were no adverse events leading to treatment discontinuation. Abnormal laboratory changes were observed in 2 subjects of the process E group (ALT increased), for which causal relationships with the investigational product were not ruled out.

On the basis of the above, PMDA has concluded that the changes of the drug product used in clinical studies do not affect the evaluation of bridging.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

Results of the following studies were submitted as evaluation data: a phase I dose-escalation study (5.3.3.2-1) and a phase II study (5.3.5.1-1) in Japanese RA patients, phase II studies in non-Japanese RA patients (5.3.5.1-7, 5.3.5.1-2, 3), population pharmacokinetic analysis (5.3.3.5-1, 2), exposure-response analysis data (5.3.4.2-1, 2), and 2 exploratory studies on immune reactions (5.3.3.1-1, 5.3.5.4-7).

Pharmacokinetic parameters are expressed as means or means ± SD unless otherwise stated.

4.(ii).A.(1) Studies in RA patients

[Japanese clinical studies]

4.(ii).A.(1).1) Phase I dose-escalation study in Japanese RA patients (5.3.3.2-1, Study IM101-034 [February 2004 to December 2005])

In an open-label dose-escalation study in 21 Japanese RA patients, abatacept (2, 8, 16 mg/kg) was administered by a single intravenous infusion. The pharmacokinetic parameters obtained

from the study are shown in Table 5. The data showed that C_{max} and AUC_{inf} increased in a dose proportional manner.

Table 5. Pharmacokinetic parameters following a single intravenous dose of abatacept (2, 8, 16 mg/kg) to Japanese RA patients

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	T_{max} (h)	CLT (mL/h/kg)	Vss (L/kg)
2 (n = 6)	36.41 (24)	4509.34 (36)	212.02 ± 76.03	1.25 [0.5, 2]	0.46 ± 0.15	0.11 ± 0.02
8 (n = 7)	161.35 (14)	21,329.99 (23)	226.85 ± 63.45	0.52 [0.5, 2]	0.38 ± 0.09	0.10 ± 0.02
16 (n = 6)	318.01 (43)	46,065.31 (44)	246.69 ± 107.13	2 [0.5, 2]	0.37 ± 0.16	0.12 ± 0.06

C_{max} and AUC_{inf} : geometric means (%CV)
$t_{1/2}$, CLT, and Vss: arithmetic means ± SD
T_{max}: the median [min, max]

Abatacept (2, 8, 16 mg/kg) was administered by multiple intravenous infusions on Days 1, 15, 29, and 57 to the same subjects who had received the single dose administration. The results of the pharmacokinetic parameters after the last dose (Day 57) are shown in Table 6, and these values were similar in profile to those following the single dose administration. C_{max} and AUC_{0-t} increased in a dose proportional manner. The accumulated index (AI) was 1.39 to 1.92, showing no marked accumulation of abatacept with multiple dose administrations. Serum abatacept concentrations on Day 57 (before dosing) and on Day 85 (28 days after the last dose) were comparable, suggesting that the serum concentration had almost reached the steady state.

Table 6. Pharmacokinetic parameters following multiple intravenous doses of abatacept (2, 8, 16 mg/kg) to Japanese RA patients (Day 57)

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)	T_{max} (h)	CLT (mL/h/kg)	Vss (L/kg)	AI
2 (n = 6)	43.49 (21)	6714.75 (35)	305.10 ± 121.57	1.27 [0.5, 6]	0.32 ± 0.10	0.11 ± 0.03	1.39 ± 0.15*
8 (n = 6)	187.54 (15)	27,271.06 (37)	231.82 ± 56.89	1.25 [0.5, 2.17]	0.31 ± 0.10	0.09 ± 0.02	1.50 ± 0.86
16 (n = 6)	454.42 (28)	69,918.13 (18)	259.00 ± 99.28	2 [0.5, 2]	0.23 ± 0.04	0.08 ± 0.02	1.92 ± 0.77

C_{max} and AUC_{0-t} : geometric means (%CV)
$t_{1/2}$, CLT, and Vss: arithmetic means ± SD
T_{max}: the median [min, max]
accumulated index (AI) = AUC_{0-t} on Day 57/AUC_{0-t} on Day 1
*: n = 4

4.(ii).A.(1).2) Japanese phase II multiple intravenous administration study in Japanese RA patients who had not adequately responded to MTX (5.3.5.1-1, Study IM101-071 [June 2006 to November 2007])

In a placebo-controlled, randomized, double-blind, parallel group, comparative study (bridging study) in 194 Japanese RA patients (56.0 ± 9.4 kg), abatacept (2, 10 mg/kg) was administered by intravenous infusion on Days 1, 15, 29, and every 28 days up to Day 141, and serum abatacept concentrations were measured immediately before each dose (trough concentration [C_{min}]), immediately after the dose and at 1 time point from 2 to 4 hours after administration on Day 85, 1 time point from Day 92 to 105, and on Day 169 (pharmacokinetic evaluable set: 128). No marked changes were observed in the serum abatacept concentrations on and after Day 57. The mean C_{min} at steady state ranged from 2.8 to 3.5 μg/mL and from 18.2 to 22.6 μg/mL at 2 and 10 mg/kg, respectively, being slightly lower than those observed in the foreign phase II study (bridging study; 4.4-6.7 μg/mL and 22.0-28.7 μg/mL, respectively).

[Foreign clinical studies]

4.(ii).A.(1).3 Foreign phase II multiple intravenous administration study in non-Japanese RA patients who had not adequately responded to DMARDs (5.3.5.1-7, Study IM103-002 [19 to 20]

In a placebo-controlled, randomized, double-blind, parallel group, comparative study in 214 non-Japanese RA patients (71.0 ± 14.6 kg), abatacept (0.5, 2, 10 mg/kg) was administered by intravenous infusion on Days 1, 15, 29, and 57 without concomitant use of DMARD. The pharmacokinetic parameters obtained from the study are shown in Table 7.

Table 7. Pharmacokinetic parameters following intravenous doses of abatacept (0.5, 2, 10 mg/kg) to non-Japanese RA patients (Days 1 and 57)

	Day 1			Day 57		
Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)
0.5 (n = 2)	13.7 (12)	1175 (15)	119.7 ± 18.4	7.5 (98)	1168 (-)[a]	161.4 ± 97.2
2.0 (n = 3)	48.5 (20)	4453 (16)	126.3 ± 28.9	57.3 (29)	5020 (37)	191.1 ± 47.4[b]
10.0 (n = 3)	269.6 (40)	22,745 (27)	129.8 ± 11.6	263.9 (25)	34,732 (23)	255.3 ± 59.0

C_{max} and AUC_{0-t}: geometric means (%CV)
$t_{1/2}$: the arithmetic mean ± SD
a, n = 1; b, n = 2

4.(ii).A.(1).4 Foreign phase II multiple intravenous administration study in non-Japanese RA patients who had not adequately responded to MTX (5.3.5.1-2, Study IM101-100 [December 2000 to June 2002])

In a placebo-controlled, randomized, double-blind, parallel group, comparative study in 339 non-Japanese RA patients (78.8 ± 19.2 kg), abatacept (2, 10 mg/kg) was administered by intravenous infusion on Days 1, 15, 30, and every 30 days thereafter, with concomitant use of MTX. The pharmacokinetic parameters from the study are shown in Table 8. C_{max} and AUC_{0-t} increased in a dose proportional manner. C_{min} was almost constant on and after Day 60 (4.4-6.7 μg/mL and 22.0-28.7 μg/mL, respectively).

Table 8. Pharmacokinetic parameters following multiple intravenous doses of abatacept (2, 10 mg/kg) to non-Japanese RA patients

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)	CLT (mL/h/kg)	Vss (L/kg)
2 (n = 15)	54.9 (29)	9573.5 (30)	324.1 ± 141.8	0.23 ± 0.13	0.07 ± 0.04
10 (n = 14)	284.2 (23)	47,624.2 (31)	314.7 ± 127.6	0.22 ± 0.09	0.07 ± 0.03

C_{max} and AUC_{0-t}: geometric means (%CV)
$t_{1/2,}$ CLT, and Vss: arithmetic means ± SD

4.(ii).A.(1).5 Foreign phase II multiple intravenous administration study in non-Japanese RA patients who had not adequately responded to etanercept (5.3.5.1-3, Study IM101-101 [February 2001 to September 2002])

In a placebo-controlled, double-blind, parallel group, comparative study in 121 non-Japanese RA patients (80.6 ± 21.0 kg), abatacept (2 mg/kg) was administered by intravenous infusion on Days 1, 15, 30, and every 30 days thereafter, with concomitant use of etanercept (25 mg, subcutaneous administration twice weekly). The pharmacokinetic parameters obtained from the study are shown in Table 9. The mean C_{min} at steady state ranged from 3.3 to 4.8 μg/mL.

Table 9. Pharmacokinetic parameters following multiple intravenous doses of abatacept (2 mg/kg) to non-Japanese RA patients

Dose (mg/kg)	C_{max} (μg/mL)	AUC_{0-t} (μg·h/mL)	$t_{1/2}$ (h)	CLT (mL/h/kg)	Vss (L/kg)
2 (n = 6)	71.5 (21%)	13,708.4 (23%)	316.1 ± 87.4	0.15 ± 0.03	0.05 ± 0.01

C_{max} and AUC_{0-t}: geometric means (%CV)
$t_{1/2,}$ CLT, and Vss: arithmetic means ± SD

4.(ii).A.(2) Population pharmacokinetic analysis

4.(ii).A.(2).1) PPK analysis in non-Japanese RA patients (5.3.3.5-1)

PPK analysis was performed by NONMEM (version V) using serum abatacept concentration data obtained at 2148 measuring time points from a total of 388 non-Japanese RA patients in foreign clinical studies (IM103-002, 100, 101, 102, 029, 031). Using, as the basic model, a 2-compartment model with zero-order absorption and first-order elimination, variation factors (body weight, age, sex, disease condition, hepatic function, renal function, concomitant drugs) for CL, V1, and V2 were investigated. As a result, body weight was selected as the variation factor for CL.

The population mean of CL was estimated to be 0.28 mL/h/kg (0.54 L/day), and the population mean of Vss (sum of V1 and V2) to be 8.05 L, at around the mean body weight of 80 kg. Estimated pharmacokinetic parameters at steady state in non-Japanese RA patients at the fixed dose based on body weight were as follows: AUC, 33,747 ± 9425 μg hours/mL; C_{max}, 248 ± 53 μg/mL; and C_{min}, 16.6 ± 8.7 μg/mL.

4.(ii).A.(2).2) PPK analysis in Japanese RA patients (5.3.3.5-2.2)

PPK analysis was performed by NONMEM (version VII) using serum abatacept concentration data collected at 2535 measuring time points from a total of 344 Japanese RA patients in Japanese clinical studies (IM101-071, 129). Using, as the basic model, a 2-compartment model with zero-order absorption and first-order elimination, variation factors (body weight, age, sex, disease condition, hepatic function, renal function, concomitant drugs) for CL, V1, and V2 were investigated. As a result, body weight was selected as the variation factor for V1 and V2, and body weight and GFR as the variation factors for CL.

The population means of Vss and CL at the median body weight of 54.6 kg and reference GFR value of 90 mL/min/1.73 m^2 were estimated to be 0.09 L/kg (4.82 L) and 0.264 mL/h/kg (0.346 L/day), respectively. Estimated pharmacokinetic parameters at steady state in Japanese RA patients at 10 mg/kg and at the fixed dose based on body weight are shown in Table 10. All parameters were comparable between the two administration methods.

Table 10. Estimated pharmacokinetic parameters in Japanese RA patients at 10 mg/kg or at the fixed dose based on body weight

Dose	AUC_{ss} (μg·h/mL)	C_{ss_max} (μg/mL)	C_{ss_min} (μg/mL)
10 mg/kg (n = 61)	41,005 ± 8410	225.44 ± 38.87	18.44 ± 7.33
Fixed dose based on body weight (n = 216)	48,475 ± 12,631	235.85 ± 43.18	24.11 ± 10.47

Mean ± SD. Fixed dose based on body weight: 500 mg at <60 kg, 750 mg at ≥60 kg and ≤100 kg, 1000 mg at >100 kg

4.(ii).A.(3) Exposure-response (E-R) analysis

4.(ii).A.(3).1) E-R analysis in non-Japanese RA patients (5.3.4.2-1)

In order to evaluate the relationship between the percentage of subjects achieving a 20%

improvement in the American College of Rheumatology criteria (ACR 20 response) and the estimated C_{min} at steady state in non-Japanese RA patients at 6 months of treatment with abatacept, E-R analysis was performed using a logistic regression model. C_{min} at steady state was estimated by the PPK model (5.3.3.5-1). The logistic regression model was constructed from the data collected from a total of 762 subjects (placebo, 457 subjects; 2 mg/kg, 128 subjects; 10 mg/kg or fixed dose based on body weight, 177 subjects) in foreign clinical studies (IM101-029, 100, 101, 102). The curve of the estimated ACR 20 response plotted against C_{min} at steady state is shown in Figure 1. The maximum estimated ACR 20 response following administration of abatacept for 6 months was 0.73. The estimated ACR 20 responses at the 5th, 50th, and 95th percentiles of the estimated C_{min} following 10 mg/kg administration (5.0, 14.1, 31.5 μg/mL, respectively) were 0.52, 0.62, and 0.67, respectively, corresponding to approximately 71%, 85%, and 92% of the maximum estimate (0.73).

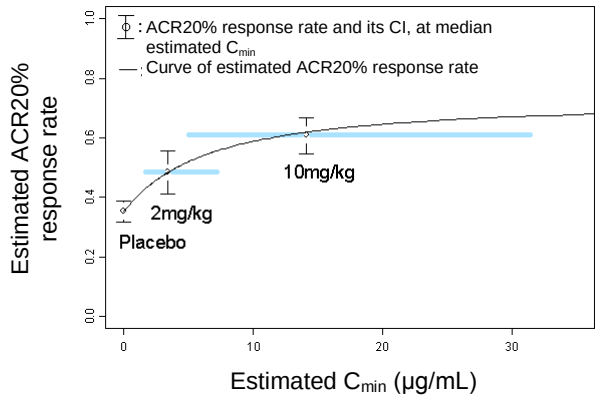


Figure 1. Curve of estimated ACR20 response for estimated C_{min} at steady state at 6 months of treatment with abatacept
Horizontal bar passing through the white dot: range of 5th to 95th percentile of estimated C_{min}

4.(ii).A.(3).2) E-R analysis in Japanese RA patients (5.3.4.2-2)

In order to evaluate the relationship between the ACR 20 response and observed C_{min} at steady state in Japanese RA patients at 6 months of treatment with abatacept, E-R analysis was performed by a logistic regression model. The logistic regression model was constructed from the data collected from a total of 194 subjects (placebo, 66 subjects; 2 mg/kg, 67 subjects; 10 mg/kg, 61 subjects) in the phase II study (IM101-071). The curve of the estimated ACR 20 response plotted against observed C_{min} is shown in Figure 2. The estimated ACR 20 response (95% CI) was 0.68 (0.47-0.83) to 0.82 (0.70-0.90) within the C_{min} range observed at 10 mg/kg (4.09-55.22 μg/mL) and 0.77 (0.65-0.86) at the median C_{min} (20.41 μg/mL). Among subjects who achieved ACR 20 response at 6 months after 10 mg/kg administration in Study IM101-071, 91.5% showed C_{min} that exceeded 10 μg/mL, the level expected to exhibit the maximum clinical effect. In the long-term extension study (IM101-129), 92.2% of subjects with C_{min} > 10 μg/mL achieved ACR 20 response.

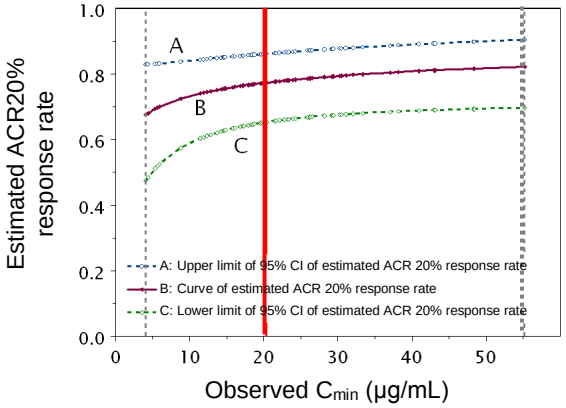


Figure 2. Curve of estimated ACR 20 response for C_{min} at 6 months of treatment with abatacept in 10 mg/kg group Vertical solid line, median C_{min}; vertical dotted lines, maximum C_{min} and minimum C_{min} above the lower limit of quantitation

4.(ii).A.(4) Immunogenicity (5.3.5.3-1)

4.(ii).A.(4).1) Immunogenicity in foreign clinical studies

In 7 foreign double-blind studies[2] and 7 open-label studies[3] (3985 subjects in total) conducted in non-Japanese RA patients, the percentage of antibody positive subjects was 6.3% (252 of 3985 subjects) (anti-abatacept antibody, 4.6% [178 of 3868 subjects]; anti-CTLA4-T antibody, 2.1% [82 of 3985 subjects]). The percentages of antibody positive subjects during the treatment period and during the follow-up period were 4.8% (187 of 3877 subjects) and 5.5% (103 of 1888 subjects), respectively, and showed a slightly higher tendency in patients who discontinued the study. Of 48 patients who were judged as anti-CTLA4-T positive and evaluated for neutralizing antibody activity, 22 were found to have neutralizing antibodies.

Results of the investigation on the relationship between antibody production and safety showed that the safety profile for the 252 immunogenicity-positive subjects was similar to that of the entire population. Adverse events immediately after intravenous infusion (i.e., within 1 hour after the start of administration) were observed in 28 subjects, and 1 of these subjects had an anaphylactic reaction. Other adverse events included hypertension or blood pressure increased (9 subjects), dizziness (6 subjects), injection site reactions such as swelling, pain, and extravasation (5 subjects), headache or procedural headache (4 subjects), nausea (2 subjects), and hypotension or blood pressure decreased (2 subjects), but none were considered to be typical hypersensitivity reactions. Thus, there were no findings that suggested a definite relationship between antibody production and the occurrence of adverse events caused by intravenous infusion.

As regards the relationship between antibody production and efficacy, 83% (55 of 66 subjects) of subjects who had achieved ACR 20 response before antibody production maintained the improved state even after antibody production, showing no consistent tendency between immunogenicity and efficacy, although there were limited number of subjects evaluable for efficacy before and after antibody production. As for pharmacokinetics, CL and V1 estimated by PPK analysis were comparable between subjects who are immunogenicity-positive and those who are immunogenicity-negative, with the C_{min} of positive subjects (5-20 μg/mL in most subjects) being comparable to the 5th to 95th percentile of C_{min} in negative subjects (4-20 μg/mL).

[2]Studies IM101-100, 101, 102, 029, 031, 043, and 064

[3]Studies IM101-100LT, 101LT, 029LT, 102LT, 031LT, 043LT, and 064LT

Neutralizing antibody was detected only in a limited number of subjects, which made it difficult to fully investigate the relationship between neutralizing antibody activity and efficacy or pharmacokinetics.

4.(ii).A.(4).2) Immunogenicity in Japanese clinical studies

In Japanese clinical studies (Studies IM101-034, 071, and 129; 231 subjects in total) conducted in Japanese RA patients, the percentage of antibody positive subjects was 14.3% (33 of 231 subjects) (anti-abatacept antibody, 3.5% [8 of 231 subjects]; anti-CTLA4-T antibody, 11.3% [26 of 231 subjects]). The percentages of antibody positive subjects during the treatment period, during the follow-up period, and during the transitional period within treatment or between treatments including treatment discontinuation were 3.0% (7 of 231 subjects), 26.3% (5 of 19 subjects), and 17.5% (25 of 143 subjects), respectively, and the percentage of antibody positive subjects was higher after study discontinuation or treatment discontinuation than during treatment. Neutralizing antibody activity was evaluated in 25 subjects, 8 of whom showed this activity.

No noteworthy tendency or relationship was observed between immunogenicity and safety in antibody positive subjects. In Study IM101-129, 69.2% (18 of 26 subjects) of immunogenicity positive subjects achieved ACR 20 response at week 48, showing no definite relationship between immunogenicity and efficacy. Serum abatacept concentrations in the immunogenicity positive subjects were within the range of concentrations observed in negative subjects, showing no tendency for a marked decrease in positive subjects.

4.(ii).A.(5) Exploratory studies on pharmacodynamics and immune reaction

4.(ii).A.(5).1) Evaluation of biomarkers

Biomarkers (sIL-2R, RF, sICAM-1, E-secretin, IL-6, and TNF-α) were evaluated in an exploratory manner at 6 months and 1 year of treatment in a foreign phase II study (IM101-100) and at 6 months of treatment in a Japanese phase II study (IM101-071). In both the Japanese and the foreign studies, 5 biomarkers other than TNF-α showed dose-dependent improvements from baseline.

4.(ii).A.(5).2) Effect of abatacept on immune reaction in synovial tissue (5.3.5.4-7, Study IM101-015 [December 2003 to April 2005])

An open-label, uncontrolled study was conducted in 16 non-Japanese RA patients to compare synovial tissue markers before and after abatacept administration. Abatacept was administered at a fixed dose based on body weight on Days 1, 15, 29, 57, 85, and 113. As a result, decreased infiltration of inflammatory cells (median decrease: $CD20^+$, 71%; $CD79^+$, 100%; $CD68^+$, 12%; ICAM, 21%) and decreased IFN-γ (52% in geometric mean) were observed in the synovial tissue (the sublining layer of the synovial tissue) at 4 months of treatment. Also, in patients who responded to the treatment, IL−1β, IL−6, MMP−1, MMP−3, and RANK decreased substantially as compared with nonresponsive patients.

4.(ii).A.(5).3) Exploratory study to evaluate the effect of abatacept on antibody responses after vaccination with tetanus toxoid and 23-valent pneumococcal vaccine in healthy adult subjects (5.3.3.1-1, Study IM101-049 [August 2004 to January 2005])

A randomized, open-label, parallel group, comparative study was conducted in non-Japanese healthy adult male subjects (target sample size of 80 subjects [20 subjects per group]) to evaluate the effect of abatacept administration on antibody responses to vaccinations with tetanus toxoid and 23-valent pneumococcal vaccine.

Group A was to receive the vaccine (intramuscular administration of 0.5 mL tetanus toxoid or 23-valent pneumococcal vaccine, same hereafter) on Day 1 only, group B to receive the vaccine on Day 1 and abatacept (750 mg single dose intravenous infusion, same hereafter) on Day 14, and group C to receive abatacept on Day 1 and the vaccine on Day 14, and group D to receive abatacept on Day 1 and the vaccine on Day 56.

A total of 80 subjects treated (20 subjects per group) were all included in the safety analysis.

In all groups, antibody titers increased after vaccination with tetanus toxoid or pneumococcal vaccine ≥2 fold as compared with the titer before the vaccination, suggesting that single dose administration of abatacept did not inhibit the immunologic competence of healthy subjects. However, the antibody titer was lower in groups C and D receiving the vaccine at 14 and 56 days, respectively, after abatacept administration, as compared with group A.

Treatment-emergent adverse events (except abnormal laboratory changes) were observed in 47.4% (9 of 19 subjects) in group B (after abatacept administration), in 35.0% (7 of 20 subjects) in group C, and in 65.0% (13 of 20 subjects) in group D. The most common adverse events were headache (4 subjects in group B, 2 subjects in group C, 6 subjects in group D), injection site pain (0 in group B, 2 subjects in group C, 4 subjects in group D), and viral infection (1 subject in group B, 1 subject in group C, 4 subjects in group D). No deaths occurred. Urticaria generalised was observed as a serious adverse event in 1 subject in group D immediately after abatacept administration. A causal relationship with the investigational product was not ruled out, but the urticaria eventually resolved. Abnormal laboratory changes, observed in some subjects, were all mild or moderate in severity.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Racial differences in pharmacokinetics of abatacept

In light of the finding that the trough concentration of abatacept tended to be low in the Japanese IM101-071 study as compared with the concentration observed in the foreign IM101-100 study, PMDA asked the applicant to explain the effect of racial differences on the pharmacokinetics of abatacept.

The applicant explained as follows:
Comparison between the Japanese IM101-071 study and the foreign IM101-100 study showed that the trough concentration at steady state tended to be lower in Japanese subjects than in non-Japanese subjects. Differences in patient characteristics such as body weight and GFR are thought to contribute to this difference. However, given that the dose-response relationship of the efficacy is similar between the two studies, showing no tendency for a lower ACR response in Japanese patients as compared with non-Japanese patients, and that no dose-dependent adverse events were observed in either of the studies, the difference in trough concentration between the 2 studies is considered to be within a range that does not affect either the efficacy or the safety of abatacept.

The applicant also explained as follows:
PPK analysis was performed on the pooled data of these 2 studies (128 Japanese, 164 non-Japanese), and the CL of the final PPK model[4] obtained (body weight was selected as the covariate of CL, V1, and V2, and GFR was selected as the covariate of CL) was evaluated with the inclusion of the racial effect. The effect of ethnic differences was estimated to be low, at 11.3% (95% CI, 1.3%-20.3%). Moreover, when AUC, C_{max} and C_{min} were estimated at steady state following the administration of a fixed dose based on body weight, the median ethnic differences were 6%, 11%, and 14%, respectively, and the ranges of the distribution of each

[4] Constructed employing a model similar to that used for PPK analysis of combined Japanese phase II and III studies (5.3.3.5-2).

parameter mostly overlapped. These results suggest that there are no clinically significant racial differences.

PMDA accepted the above response.

4.(ii).B.(2) Factors related to antibody production

PMDA asked the applicant to assess the effect of concomitant use of MTX, treatment duration, abatacept concentration, etc., on the production of anti-abatacept antibody and anti-CTLA4-T antibody.

The applicant explained as follows:

In Japanese clinical studies, most patients were concomitantly administered MTX, precluding the investigation of the effect of MTX on antibody production. In foreign clinical studies, the antibody-positive rate was 2.3% in patients with concomitant use of MTX and 1.4% in those without concomitant use of MTX, suggesting that concomitant use of MTX did not affect the percentage of immunogenicity-positive subjects. When annual immunogenicity positive rate during the 5-year treatment period (per 100 person-years [95% CI]) were investigated based on the pooled results of foreign long-term extension studies, these rate showed no clear trend: 0.86 [0.58, 1.24] in the first, 1.60 [1.14, 2.19] in the second, 2.45 [1.80, 3.25] in the third, 1.94 [1.32, 2.75] in the fourth, and 2.38 [1.70, 3.24] in the fifth year, which suggested that treatment duration did not affect immunogenicity. As regards the effect of the blood concentration of abatacept, immunogenicity-positive and negative subjects showed similar pharmacokinetics, suggesting that serum abatacept concentrations during the treatment period do not affect the percentage of immunogenicity-positive subjects. However, the immunogenicity positive rate tended to increase in patients in whom abatacept administration was discontinued or suspended for a relatively long period of time. Generally, the incidence increased when administration was discontinued for approximately 4 to 5 times the elimination half-life ($t_{1/2}$), which raises the possibility that the antibody positive rate may increase when the serum abatacept concentration is low, at around 1 μg/mL. When abatacept administration was resumed in patients who had become positive for immunogenicity during the withdrawal period, they showed no tendency for an increase in serious adverse events or adverse events immediately after administration, although findings have been obtained from only a limited number of patients as yet.

PMDA considers as follows:

Judging from the submitted data and the above responses, there appear to be no clinically significant problems associated with anti-abatacept or anti-CTLA4-T antibody at present. However, given that no thorough investigation has been conducted on the relationship between the neutralizing antibody activity and efficacy or pharmacokinetics, and that the percentage of patients with neutralizing antibody activity was relatively high (≥40%) among those who were antibody positive and evaluable for neutralizing antibody activity, further investigations are required, such as measurement of antibodies and neutralizing antibody activity in patients who show significantly decreased efficacy during treatment in the post-marketing surveillance. In addition, patients who show a serious allergic reaction such as anaphylaxis should undergo antibody test to the possible extent to investigate the relationship between the allergic reaction and antibody production.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

Results of the following studies were submitted as evaluation data for efficacy and safety: a Japanese phase I study (5.3.3.2-1, IM101-034), a Japanese phase II study (5.3.5.1-1, IM101-071), a Japanese phase III long-term administration study (5.3.5.2-1, IM101-129), foreign phase II studies (5.3.5.1-2, IM101-100; 5.3.5.1-3, IM101-101, etc.), foreign phase III

studies (5.3.5.1-4, IM101-102; 5.3.5.1-5, IM101-029; 5.3.5.1-6, IM101-031, etc.), and foreign long-term extension studies (5.3.5.2-2, IM101-100LT; 5.3.5.2-3, IM101-101LT; 5.3.5.2-4, IM101-102LT; 5.3.5.2-5, IM101-029LT; 5.3.5.2-6, IM101-031LT).

[Complete clinical data package]
This application is based on the bridging concept.

In the applicant's view, the data from foreign clinical studies can be extrapolated to Japanese RA patients, for the following reasons: (a) pharmacokinetics of abatacept were similar between Japanese and non-Japanese subjects, (b) the ACR 20, ACR 50, and ACR 70 responses at 6 months were similar between the Japanese IM101-07 study and the foreign IM101-100 study, and (c) the incidences of adverse events were similar between the IM101-071 study and the IM101-100 study. The clinical data package of the application consists of the following data, as shown in Figure 3.

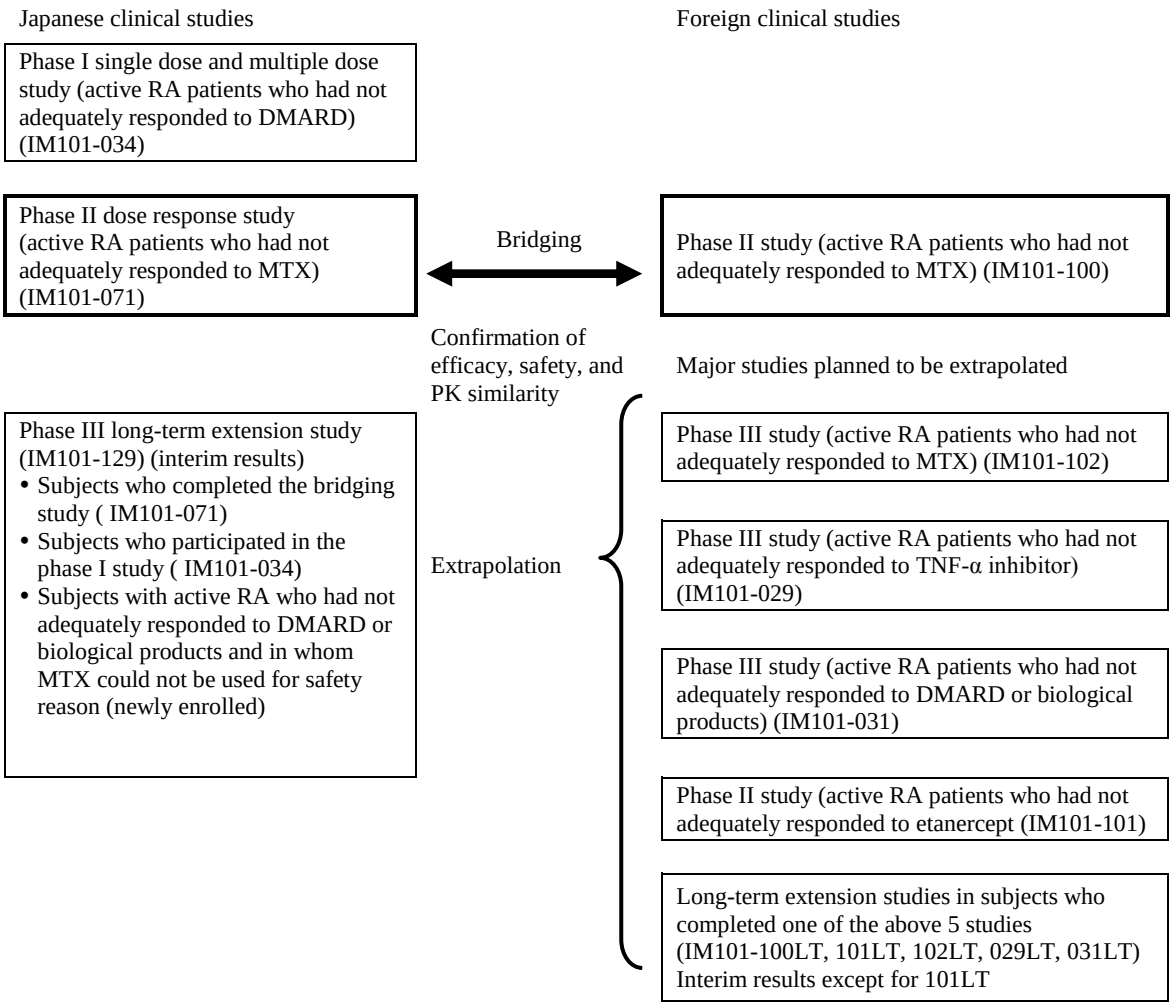


Figure 3. Clinical data package

4.(iii).A Summary of the submitted data

4.(iii).A.(1) Results of major clinical studies conducted in Japan

4.(iii).A.(1).1) Phase I dose-escalation study in Japanese RA patients (5.3.3.2-1, IM101-034 [February 2004 to December 2005])

An open-label, dose-escalation study was conducted in Japanese patients[5] (target sample size of 21 subjects [7 subjects per group]) with active RA being treated with a DMARD or an immunosuppressive agent in order to investigate the safety, efficacy, and pharmacokinetics of abatacept following a single dose or multiple intravenous doses [see "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetics].

In the single dose administration phase, abatacept was to be administered by intravenous infusion at the dose levels of 2 mg/kg (Step 1), 8 mg/kg (Step 2) or 16 mg/kg (Step 3). In the study, patients were to start treatment from Step 1 and all treated patients were to be evaluated for safety and tolerability up to Day 57. Once the Step 1 treatment was confirmed to have no safety problems, the study was to proceed to the next step in the single dose phase, then to the multiple dose phase where the patients who have received a single dose were to be administered multiple doses at the same dose level. In the multiple dose phase, each dose was to be administered to patients on Days 1, 15, 29, and 57, and the patients were to to be evaluated for safety by Day 127.
A total of 21 subjects were treated (8 subjects in the 2 mg/kg group [4 subjects receiving both single and multiple doses, 2 subjects receiving a single dose only, 2 subjects receiving multiple doses only[6]], 7 subjects in the 8 mg/kg group [6 subjects receiving both single and multiple doses, 1 subject receiving a single dose only], 6 subjects in the 16 mg/kg [6 subjects receiving both single and multiple doses]) and all were included in the safety analysis.

The ACR 20 response at Day 85 of the multiple dose phase, one of the efficacy endpoints, was 16.7% (1 of 6 subjects) in the 2 mg/kg group, 33.3% (2 of 6 subjects) in the 8 mg/kg group, and 50.0% (3 of 6 subjects) in the 16 mg/kg group.

Adverse events were observed in 17 of 19 subjects (5 of 6 subjects in the 2 mg/kg group, 6 of 7 subjects in the 8 mg/kg group, 6 of 6 subjects in the 16 mg/kg group) during the single dose phase and in 18 of 18 subjects in the multiple dose phase. No deaths occurred. Subcutaneous haematoma was observed as a serious adverse event in 1 subject of the 2 mg/kg group during the multiple dose phase; a causal relationship of this adverse event with the investigational product was ruled out. There were no adverse events leading to treatment discontinuation.

Adverse drug reactions (including abnormal laboratory changes) were observed in 16 of 19 subjects (4 of 6 subjects in the 2 mg/kg group, 6 of 7 subjects in the 8 mg/kg group, 6 of 6 subjects in the 16 mg/kg group) in the single dose phase and in 18 of 18 subjects in the multiple dose phase. The most common adverse events that occurred during the single dose phase included nasopharyngitis (1 subject in the 2 mg/kg group, 2 subjects in the 8 mg/kg group, 0 in the 16 mg/kg group; same order applies hereafter), blood pressure increased (0, 2 subjects, 2 subjects), heart rate increased (0, 0, 2 subjects), hypoaesthesia (0, 2 subjects, 0), white blood cell count increased (1 subject, 2 subjects, 3 subjects), lymphocyte count decreased (2 subjects, 2 subjects, 1 subject), white blood cells urine positive (0, 4 subjects, 2 subjects), blood cholesterol increased (0, 1 subject, 3 subjects), and protein urine present (0, 0, 2 subjects). The most common events that occurred during the multiple dose phase included stomatitis (1 subject, 0, 2 subjects), nasopharyngitis (3 subjects, 0, 0), blood pressure systolic increased (3 subjects, 2 subjects, 2 subjects), blood pressure increased (2 subjects, 2 subjects, 0), blood pressure

[5] Patients with ≥6 tender joint counts, ≥3 swollen joint counts, and erythrocyte sedimentation rate of ≥28 mm/h or CRP ≥1.0 mg/dL

[6] Two patients discontinued the study after the end of the single dose phase due to aggravations of their disease conditions. Therefore, other 2 patients were added to the study in the multiple dose phase.

diastolic increased (0, 2 subjects, 0), white blood cells urine positive (3 subjects, 1 subject, 1 subject), and blood cholesterol increased (0, 1 subject, 3 subjects).

The applicant explained that above results demonstrated the tolerability of abatacept in Japanese RA patients when the drug was administered as a single dose or multiple doses up to 16 mg/kg.

4.(iii).A.(1).2) Phase II study in Japanese RA patients who had not adequately responded to MTX (5.3.5.1-1, IM101-071 [June 2006 to November 2007]) (bridging study)

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted in RA patients who had not adequately responded to MTX[7] (target sample size of 60 subjects per group, 180 subjects in total) to investigate the dose response of abatacept used concomitantly with MTX.

Abatacept (2, 10 mg/kg) or placebo was to be administered by intravenous infusion on Days 1, 15, 29, and every 28 days up to Day 141. A fixed dose (6-8 mg/week) of MTX was to be concomitantly administered.

A total of 194 treated patients (67 subjects in 2 mg/kg group, 61 subjects in 10 mg/kg group, 66 subjects in placebo group) were all included in the efficacy and the safety analysis.

The primary efficacy endpoint was the proportion of subjects achieving an ACR 20 response at Day 169 of administration. If a significant dose response was observed by Cochran-Armitage's trend test, a between-group comparison was to be made by employing sequential tests, first abatacept 10 mg/kg vs. the placebo group, then the abatacept 2 mg/kg group vs. the placebo group. Results showed a significant dose response ($P < 0.001$, Cochran-Armitage's trend test). The ACR 20 response was higher in both the 10 mg/kg and the 2 mg/kg group than in the placebo group, as shown in Table 11. The ACR 50 and 70 responses, the secondary endpoints, are shown in Table 11.

Table 11. ACR 20, 50 and 70 responses on Day 169 of administration

	Abatacept group		Placebo group (66 subjects)	Difference from placebo group [95% CI]	
	10 mg/kg group (61 subjects)	2 mg/kg group (67 subjects)		10 mg/kg group	2 mg/kg group
ACR 20 response	77.0 (47)	62.7 (42)	21.2 (14)	55.8 [41.4, 70.3] $P < 0.001$*	41.5 [26.3, 56.7] $P < 0.001$*
ACR 50 response	45.9 (28)	37.3 (25)	6.1 (4)	39.8 [26.1, 53.6] $P < 0.001$*	31.3 [18.3, 44.2] $P < 0.001$*
ACR 70 response	21.3 (13)	16.4 (11)	0 (0)	21.3 [11.0, 31.6] $P < 0.001$*	16.4 [7.5, 25.3] $P = 0.002$*

% (number of subjects). *: χ^2 test

Adverse events (except abnormal laboratory changes) were observed in 73.1% (49 of 67 subjects) in the 2 mg/kg group, 72.1% (44 of 61 subjects) in the 10 mg/kg group, and 62.1% (41 of 66 subjects) in the placebo group. No deaths occurred. The incidence of serious adverse events was 3.0% (2 of 67 subjects) in the 2 mg/kg group (calculus ureteric, cholelithiasis), 8.2% (5 of 61 subjects) in the 10 mg/kg group (arthritis, aplasia pure red cell/parvovirus

[7] Patients who had been treated with MTX (6-8 mg/week) for ≥12 weeks and had ≥10 swollen joint counts, ≥12 tender joint counts, and CRP ≥1 mg/dL

infection/upper respiratory tract inflammation, spinal compression fracture, abdominal pain/vomiting, spinal compression fracture/osteoporosis in 1 subject each), and 9.1% (6 of 66 subjects) in the placebo group (rheumatoid arthritis in 2 subjects, Vernet's syndrome, fibula fracture/tibia fracture, acute myocardial infarction, dizziness in 1 subject each). Causal relationships with the investigational product were not ruled out for aplasia pure red cell/parvovirus infection/upper respiratory tract inflammation, abdominal pain/vomiting in the 10 mg/kg group or for myocardial infarction in the placebo group, but all the outcome of these events resolved or were resolving. Adverse events leading to treatment discontinuation occurred in 3.0% (2 of 66 subjects) in the placebo group (Vernet's syndrome, acute myocardial infarction).

Adverse drug reactions (except abnormal laboratory changes) were observed in 59.7% (40 of 67 subjects) in the 2 mg/kg group, 49.2% (30 of 61 subjects) in the 10 mg/kg group, and 34.8% (23 of 66 subjects) in the placebo group. The most common adverse events observed are summarized in Table 12.

Table 12. Adverse drug reactions that occurred in at least 2% of subjects in either group

	Abatacept group		Placebo group
Preferred term	10 mg/kg (N = 61)	2 mg/kg (N = 67)	(n = 66)
Nasopharyngitis	9 (14.8)	14 (20.9)	4 (6.1)
Pyrexia	1 (1.6)	0	3 (4.5)
Cystitis	0	3 (4.5)	0
Blood pressure increased	1 (1.6)	3 (4.5)	0
Headache	2 (3.3)	4 (6.0)	2 (3.0)
Upper respiratory tract inflammation	4 (6.6)	3 (4.5)	2 (3.0)
Stomatitis	2 (3.3)	2 (3.0)	1 (1.5)
Diarrhoea	1 (1.6)	1 (1.5)	2 (3.0)
Dizziness	2 (3.3)	2 (3.0)	0
Feeling abnormal	1 (1.6)	2 (3.0)	0
Eczema	2 (3.3)	0	1 (1.5)
Tinea pedis	0	2 (3.0)	1 (1.5)
Cough	0	2 (3.0)	1 (1.5)
Pharyngolaryngeal pain	0	2 (3.0)	1 (1.5)
Blood pressure decreased	0	1 (1.5)	2 (3.0)
Weight decreased	2 (3.3)	0	0
Glossitis	0	2 (3.0)	0
Flushing	0	2 (3.0)	0
Hypertension	0	2 (3.0)	0

Number of subjects (%)

Abnormal laboratory changes were observed in 37.3% (25 of 67 subjects) in the 2 mg/kg group, 34.4% (21 of 61 subjects) in the 10 mg/kg group, and 31.8% (21 of 66 subjects) in the placebo group. Abnormal laboratory changes, for which a causal relationship to the investigationa product cannot be ruled out, were observed in 22.4% (15 of 67 subjects) in the 2 mg/kg group, 23.0% (14 of 61 subjects) in the 10 mg/kg group, and 19.7% (13 of 66 subjects) in the placebo group. The most common events are shown in Table 13.

Table 13. Treatment-related abnormal laboratory changes that occurred in at least 2% of subjects in either group

Preferred term	Abatacept group		Placebo group
	10 mg/kg (N = 61)	2 mg/kg (N = 67)	(n = 66)
ALT increased	6 (9.8)	5 (7.5)	1 (1.5)
AST increased	3 (4.9)	2 (3.0)	1 (1.5)
Lymphocyte count decreased	1 (1.6)	3 (4.5)	6 (9.1)
White blood cell count increased	3 (4.9)	4 (6.0)	3 (4.5)
Glucose urine present	0	2 (3.0)	0
Blood glucose decreased	0	0	2 (3.0)
White blood cells urine positive	0	0	2 (3.0)

Number of subjects (%)

Thus, on the basis of the findings that the ACR 20 response at Day 169 of administration, the primary endpoint, showed a significant dose response among the placebo group and abatacept 2 and 10 m/kg groups and that abatacept was well tolerated at both 2 and 10 mg/kg, the applicant explained that 10 mg/kg was considered to be the appropriate clinical dose for Japanese RA patients, and that the dose responses of abatacept were similar in this study and the foreign phase II dose-response study IM101-100.

4.(iii).A.(2) Results of major foreign clinical studies

4.(iii).A.(2).1) Phase II study in non-Japanese RA patients who had not adequately responded to MTX (5.3.5.1-2, IM101-100 [December 2000 to June 2002]) (bridging counterpart)

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted in patients with active RA who had not adequately responded to MTX[8] (target sample size of 321 subjects [107 subjects per group]) to investigate the efficacy and safety of abatacept at 2 dose levels under concomitant use of MTX.

Abatacept (2, 10 mg/kg) or placebo was to be administered by intravenous infusion on Days 1, 15, 30, and every 30 days thereafter. The treatment duration was 1 year. A fixed dose (10-30 mg/week) of MTX was to be concomitantly administered up to Day 180, and adjustment of the MTX dose was allowed (≤30 mg/week) on or after Day 181.

A total of 339 treated patients (105 subjects in the 2 mg/kg group, 115 subjects in the 10 mg/kg group, 119 subjects in the placebo group) were included in the intent-to-treat (ITT) population and subjected to efficacy and safety analysis.

The ACR 20 response at 6 months of treatment, the primary endpoint, is shown in Table 14. The response rate in the abatacept 10 mg/kg group was significantly higher than in the placebo group, whereas no significant difference was observed in the response rate between the 2 mg/kg group and the placebo group[9]. The ACR 50 and 70 responses at 6 months of treatment, the secondary endpoints, are shown in Table 14, and the responses in the 2 mg/kg and 10 mg/kg groups were both significantly higher than those in the placebo group.

Table 14. ACR 20, 50, and 70 responses at 6 months of treatment

	Abatacept group		Placebo group (119 subjects)	Difference from placebo [95% CI]	
	10 mg/kg group (115 subjects)	2 mg/kg group (105 subjects)		10 mg/kg group	2 mg/kg group
ACR 20 response	60.9 (70)	41.9 (44)	35.3 (42)	25.6 [12.8, 38.4] $P < 0.001$*	6.6 [-6.2, 19.4] $P = 0.31$*
ACR 50 response	36.5 (42)	22.9 (24)	11.8 (14)	24.8 [13.8, 35.7] $P < 0.001$*	11.1 [1.2, 20.9] $P = 0.027$*
ACR 70 response	16.5 (19)	10.5 (11)	1.7 (2)	14.8 [7.5, 22.2] $P < 0.001$*	8.8 [2.7, 14.9] $P = 0.005$*

% (number of subjects). *: χ^2 test

Adverse events (except abnormal laboratory changes) were observed in 99.0% (104 of 105 subjects) in the 2 mg/kg group, 90.4% (104 of 115 subjects) in the 10 mg/kg group, and 94.1% (112 of 119 subjects) in the placebo group. Death occurred in 1 subject of the 2 mg/kg group (caused by combined factors including cardiac failure congestive, renal failure, and hepatic failure). A causal relationship of this death with the investigational product was ruled out. Serious adverse events were observed in 18.1% (19 of 105 subjects) in the 2 mg/kg group, 12.2% (14 of 115 subjects) in the 10 mg/kg group, and 16.0% (19 of 119 subjects) in the placebo group. The only serious adverse event that occurred in at least 2 subjects of either abatacept group was chest pain (4 subjects in 2 mg/kg group, 1 subject in 10 mg/kg group, 0 in placebo group). Serious adverse events, for which a causal relationship to the investigationa product can not be ruled out, were observed in 4.8% (5 of 105 subjects) in the 2 mg/kg group,

[8] Patients who had been treated with MTX (10-30 mg/week) for ≥6 months and had ≥10 swollen joint counts, ≥12 tender joint counts, and CRP ≥ 1.0 mg/dL

[9] ACR 20% response rate was first compared between the 10 mg/kg group and the placebo group and, if a significant difference was observed, the rate was then to be compared between the 2 mg/kg group and the placebo group.

1.7% (2 of 115 subjects) in the 10 mg/kg group, and 1.7% (2 of 119 subjects) in the placebo group. Adverse events leading to treatment discontinuation were observed in 9.5% (10 of 105 subjects) in the 2 mg/kg group, 5.2% (6 of 115 subjects) in the 10 mg/kg group, and 9.2% (11 of 119 subjects) in the placebo group. The only adverse event that occurred in at least 2 subjects of either abatacept group was chest pain (2 subjects in the 2 mg/kg group).

Adverse drug reactions (except abnormal laboratory changes) were observed in 47.6% (50 of 105 subjects) in the 2 mg/kg group, 48.7% (56 of 115 subjects) in the 10 mg/kg group, and 48.7% (58 of 119 subjects) in the placebo group. Adverse drug reactions that occurred in at least 2% of subjects in either group are shown in Table 15.

Table 15. Adverse drug reactions that occurred in at least 2% of subjects in either group

	Abatacept group		Placebo group
Preferred term	10 mg/kg (N = 115)	2 mg/kg (N = 105)	(n = 119)
Nasopharyngitis	7 (6.1)	3 (2.9)	4 (3.4)
Nausea	6 (5.2)	6 (5.7)	7 (5.9)
Headache	6 (5.2)	6 (5.7)	8 (6.7)
Cough	6 (5.2)	2 (1.9)	3 (2.5)
Upper respiratory tract infection	5 (4.3)	2 (1.9)	1 (0.8)
Bronchitis	5 (4.3)	2 (1.9)	3 (2.5)
Flushing	4 (3.5)	2 (1.9)	1 (0.8)
Diarrhoea	3 (2.6)	1 (1.0)	2 (1.7)
Dyspepsia	3 (2.6)	3 (2.9)	2 (1.7)
Fatigue	3 (2.6)	1 (1.0)	4 (3.4)
Pharyngolaryngeal pain	3 (2.6)	1 (1.0)	3 (2.5)
Influenza	3 (2.6)	2 (1.9)	4 (3.4)
Vomiting	2 (1.7)	3 (2.9)	3 (2.5)
Sinusitis	2 (1.7)	3 (2.9)	4 (3.4)
Rash	2 (1.7)	1 (1.0)	3 (2.5)
Hypertension	1 (0.9)	4 (3.8)	3 (2.5)
Rheumatoid arthritis[a]	1 (0.9)	1 (1.0)	3 (2.5)
Alopecia	0	3 (2.9)	1 (0.8)

Number of subjects (%)

The most common abnormal laboratory changes were white blood cell count high (5.8% [6 of 105 subjects] in the 2 mg/kg group, 10.4% [12 of 115 subjects] in the 10 mg/kg group, 11.8% [14 of 119 subjects] in the placebo group) and creatinine high (2.9% [3 of 105 subjects] in 2 mg/kg group, 3.5% [4 of 115 subjects] in the 10 mg/kg group, 3.4% [4 of 119 subjects] in the placebo group).

On the basis of the above results, the applicant explained as follows:
In RA patients who had not adequately responded to MTX, the ACR 20 response at 6 months of treatment, the primary endpoint, was significantly higher in the 10 mg/kg group than in the placebo group, whereas the response in the 2 mg/kg was not significantly higher, although it had shown a tendency for improvement. As for the safety, both the 2 mg/kg and the 10 mg/kg dose of abatacept were well tolerated when administered for 1 year. It is appropriate that the recommended clinical dose is 10 mg/kg, based on the above results and on the findings that the serum trough concentration of abatacept in the 10 mg/kg group reached the level expected to exhibit the maximum clinical efficacy (10 μg/mL).

4.(iii).A.(2).2) Study in non-Japanese RA patients who had not adequately responded to etanercept (5.3.5.1-3, IM101-101 [February 2001 to September 2002])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted in patients with active RA who had not adequately responded to etanercept[10] (target sample size of 141 subjects [94 subjects in abatacept group, 47 subjects in placebo group]) to investigate the efficacy and safety of abatacept under concomitant use of etanercept.

Abatacept (2 mg/kg) or placebo was to be administered by intravenous infusion on Days 1, 15, and 30, and then at intervals of 30 days. The treatment duration was 12 months. Etanercept was to be concomitantly administered (25 mg, subcutaneous injection twice weekly) up to Day 180. If the swollen joint count or tender joint count decreased by ≥50% by Day 180, etanercept administration was to be discontinued.

All 121 treated patients (85 subjects in abatacept group, 36 subjects in placebo group) were included in the ITT population and were subjected to the efficacy and the safety analysis.

Modified ACR 20 response[11] after 6 months of treatment, the primary endpoint, was 48.2% (41 of 85 subjects) in the abatacept group and 30.6% (11 of 36 subjects) in the placebo group, showing no significant difference between the groups.

Adverse events (except abnormal laboratory changes) were observed in 92.9% (79 of 85 subjects) in the abatacept group and 88.9% (32 of 36 subjects) in the placebo group. No deaths occurred. Serious adverse events were observed in 16.5% (14 of 85 subjects) in the abatacept group and 2.8% (1 of 36 subjects) in the placebo group. The only serious adverse event that occurred in at least 2 subjects was cellulitis (2 subjects in the abatacept group, 0 in the placebo group). Causal relationships with the investigational product were not ruled out for 5 events in 5 subjects of the abatacept group (cellulitis, soft tissue infection, complex partial seizures, atypical chest pain, vasculitis in 1 subject each). Adverse events leading to treatment discontinuation were observed in 11.8% (10 of 85 subjects) in the abatacept group and in 2.8% (1 of 36 subjects) in the placebo group. The only event that occurred in at least 2 subjects was bronchitis (2 subjects in the abatacept group, 1 subject in the placebo group). Adverse drug reactions were observed in 62.4% (53 of 85 subjects) in the abatacept group and 47.2% (17 of 36 subjects) in the placebo group. Adverse drug reactions that occurred in at least 3% of subjects in either group are shown in Table 16.

[10] Patients who had been treated with etanercept (25 mg, subcutaneous injection, twice weekly) for ≥3 months and had ≥8 swollen joint counts and ≥10 tender joint counts (under etanercept monotherapy), or had ≥6 swollen joint counts and ≥8 tender joint counts (under concomitant use of etanercept and DMARD), regardless of CRP.

[11] Percentage of patients who achieved ≥20% improvement in the tender joint count and the swollen joint count and also achieved ≥20% improvement in 2 out of 4 ACR core set measures (patient's assessment of pain, patient's assessment of physical function, patient's global assessment of disease activity, physician's global assessment of disease activity). Since most patients showed low CRP at study screening (under etanercept administration), CRP was omitted from the ACR core set in assessing the primary endpoint.

Table 16. Adverse drug reactions that occurred in at least 3% of subjects in either group (1 year)

	Abatacept group (N = 85)	Placebo group (N = 36)
Headache	11 (12.9)	1 (2.8)
Dizziness	9 (10.6)	0
Nausea	7 (8.2)	1 (2.8)
Fatigue	7 (8.2)	3 (8.3)
Diarrhoea	6 (7.1)	1 (2.8)
Blood pressure decreased	6 (7.1)	1 (2.8)
Blood pressure increased	6 (7.1)	2 (5.6)
Bronchitis	5 (5.9)	1 (2.8)
Upper respiratory tract infection	5 (5.9)	2 (5.6)
Rash	5 (5.9)	2 (5.6)
Pharyngitis	3 (3.5)	0
Rheumatoid arthritis[a]	3 (3.5)	1 (2.8)
Sinusitis	2 (2.4)	2 (5.6)
Pruritus	1 (1.2)	2 (5.6)

Number of subjects (%); a, includes "aggravation of arthritis" but not events other than RA.

The most common abnormal laboratory changes were white blood cell count high (5.9% [5 of 85 subjects] in the abatacept group, 2.8% [1 of 36 subjects] in the placebo group), serum potassium high (5.9% [5 of 85 subjects] in the abatacept group, 0% in the placebo group), and ALT high (3.5% [3 of 85 subjects] in the abatacept group, 0% in the placebo group).

On the basis of the above findings, the applicant explained that, in RA patients who had not adequately responded to etanercept, no significant difference was observed in the modified ACR 20 response at 6 months, the primary endpoint, between the abatacept 2 mg/kg group and the placebo group under concomitant use of etanercept, and that the incidences of serious adverse events, treatment-related serious adverse events, etc., were higher in the abatacept group than in the placebo group.

The applicant also explained that, in 205 patients who were concomitantly administered abatacept and a TNF inhibitor in foreign pivotal clinical studies including this study (IM101-100, 101, 102, 029, and 031), the incidences of infection (63.9%) and serious infection (4.4%) were higher than those observed in 136 patients who received a TNF inhibitor alone (44.9% and 1.5%, respectively), and that concomitant use of abatacept and a TNF inhibitor did not enhance treatment efficacy. The applicant therefore plans to provide cautions in the package insert against concomitant use of abatacept with a TNF inhibitor.

4.(iii).A.(2).3) Phase III study in non-Japanese RA patients who had not adequately responded to MTX (5.3.5.1-4, IM101-102 [November 2002 to June 2004])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted in RA patients who had not adequately responded to MTX[12] (target sample size of 540 subjects [360 subjects in the abatacept group, 180 subjects in the placebo group]) to investigate the efficacy and safety of abatacept under concomitant use of MTX.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) or placebo was to be administered by intravenous infusion on Days 1, 15, 29, and every 28 days thereafter, for up to 12 months (in the phase III and the long-term extension studies, fixed doses

[12] Patients who had been treated with MTX (≥15 mg/week) for ≥3 months and had ≥10 swollen joint counts, ≥12 tender joint counts, and CRP ≥ 1.0 mg/dL (under MTX monotherapy), or had ≥6 swollen joint counts and ≥8 tender joint counts regardless of CRP (under MTX and DMARD therapy).

adjusted to approximately 10 mg/kg ± 25% were used regardless of the body weights of subjects, in order to simplify the dosage regimen, thereby avoiding administration errors). A fixed dose of MTX (10-30 mg/week) was to be concomitantly administered up to Day 169, and MTX dose adjustment and addition of a DMARD were allowed on and after Day 170.

A total of 652 treated patients (433 subjects in the abatacept group, 219 subjects in the placebo group) were included in the ITT population and subjected to the safety analysis, and 638 of these subjects (424 subjects in the abatacept group, 214 subjects in the placebo group) were subjected to the efficacy analysis. Excluded were those who had been withdrawn from the study based on the judgment of the sponsor because of protocol violation (9 subjects in the abatacept group, 5 subjects in the placebo group, all at a single study site).

Three primary endpoints were set for the study, and sequential comparisons were made starting from the first primary endpoint based on the closed testing procedure. The ACR 20 response at 6 months of treatment by the evaluation of RA symptoms, the first primary endpoint, is shown in Table 17. The response was significantly higher in the abatacept group than in the placebo group. The ACR 50 and 70 responses, the secondary endpoints, are also shown in Table 17.

Table 17. ACR 20, 50, and 70 responses at 6 months of treatment

	Abatacept group (424 subjects)	Placebo group (214 subjects)	Between-group difference [95% CI]	*P* value*
ACR 20 response	67.9 (288)	39.7 (85)	28.2 [19.8, 36.7]	<0.001
ACR 50 response	39.9 (169)	16.8 (36)	23.0 [15.0, 31.1]	<0.001
ACR 70 response	19.8 (84)	6.5 (14)	13.3 [7.0, 19.5]	<0.001

* χ^2 test with continuity correction

The percentage of subjects who achieved clinically significant Health Assessment Questionnaire Disability Index (HAQ-DI) (decrease of at least 0.3 points from baseline) after 12 months, based on evaluation of physical function, the second primary endpoint, was 63.7% (270 of 424 subjects) in the abatacept group and in 39.3% (84 of 214 subjects) in the placebo group. Thus, it was significantly higher in the abatacept group than in the placebo group ($P < 0.001$, χ^2 test with continuity correction).

Joint erosion score after 12 months, measured by the Genant-modified Sharp score based on evaluation of the prevention of structural damage to joints, the third primary endpoint, is shown in Table 18. The change from baseline was significantly smaller in the abatacept group than in the placebo group.

Table 18. Joint erosion score measured by Genant-modified Sharp score at 12 months of treatment

	Abatacept group (424 subjects)	Placebo group (214 subjects)	*P* value*
Number of subjects evaluated	391	195	0.029
Mean ± SD of change from baseline	0.63 ± 1.77	1.14 ± 2.81	
Median (interquartile range)	0.00 (0.00, 1.02)	0.27 (0.00, 1.27)	

* ANOVA using the order of change from baseline as the outcome variable, treatment as the main effect, and the order of baseline as the covariate.

Adverse events (except abnormal laboratory changes) were observed in 87.3% (378 of 433 subjects) in the abatacept group and in 84.0% (184 of 219 subjects) in the placebo group. Deaths occurred in 1 subject each in the abatacept and placebo groups, both caused by sepsis. A causal relationship with abatacept was not ruled out. Serious adverse events were observed in 15.0% (65 of 433 subjects) in the abatacept group and in 11.9% (26 of 219 subjects) in the placebo group, as shown in Table 19. Causal relationships with the investigational product were not ruled out in 3.5% (15 of 433 subjects) in the abatacept group (e.g., pneumonia in 2 subjects)

and in 0.5% (1 of 219 subjects) in the placebo group (cellulitis/abscess limb). Adverse events leading to treatment discontinuation were observed in 4.2% (18 of 433 subjects) in the abatacept group and in 1.8% (4 of 219 subjects) in the placebo group. The only adverse event that occurred in at least 2 subjects in either group was hypersensitivity (2 subjects in the abatacept group, 0 in the placebo group).

Table 19. Serious adverse events that occurred in at least 2 subjects in either group

	Abatacept group (N = 433)	Placebo group (N = 219)
Rheumatoid arthritis	11 (2.5)	6 (2.7)
Arthritis	2 (0.5)	1 (0.5)
Aseptic necrosis of bone	2 (0.5)	0
Pneumonia	4 (0.9)	1 (0.5)
Bronchopneumonia	2 (0.5)	0
Diverticulitis	2 (0.5)	0
Urinary tract infection	2 (0.5)	0
Basal cell carcinoma	2 (0.5)	0
Vascular pseudoaneurysm	2 (0.5)	0
Umbilical hernia	2 (0.5)	0
Rheumatoid nodule	2 (0.5)	0
Dehydration	2 (0.5)	0
Localized osteoarthritis	1 (0.2)	2 (0.9)

Number of subjects (%)

Adverse drug reactions were observed in 49.4% (214 of 433 subjects) in the abatacept group and 47.5% (104 of 219 subjects) in the placebo group. Those that occurred in at least 2% of subjects in either group are shown in Table 20.

Table 20. Adverse drug reactions that occurred in at least 2% of subjects in either group

	Abatacept group (N = 433)	Placebo group (N = 219)
Headache	41 (9.5)	12 (5.5)
Nausea	29 (6.7)	11 (5.0)
Dizziness	19 (4.4)	10 (4.6)
Upper respiratory tract infection	18 (4.2)	4 (1.8)
Nasopharyngitis	15 (3.5)	6 (2.7)
Fatigue	14 (3.2)	7 (3.2)
Diarrhoea	12 (2.8)	8 (3.7)
Somnolence	12 (2.8)	7 (3.2)
Influenza	11 (2.5)	3 (1.4)
Urinary tract infection	10 (2.3)	3 (1.4)
Rash	10 (2.3)	1 (0.5)
Hypertension	9 (2.1)	1 (0.5)
Asthenia	5 (1.2)	5 (2.3)
Chills	4 (0.9)	7 (3.2)

Number of subjects (%)

The most common abnormal laboratory changes were white blood cell count high (10.4 % [45 of 433 subjects] in the abatacept group, 15.2% [33 of 217 subjects] in the placebo group), creatinine high (5.3% [23 of 433 subjects] in the abatacept group, 6.9% [15 of 217 subjects] in the placebo group), white blood cell count low (3.5% [15 of 433 subjects] in the abatacept group, 1.8% [4 of 217 subjects] in the placebo group), neutrophil count low (2.3% [10 of 433 subjects] in the abatacept group, 1.4% [3 of 217 subjects] in the placebo group), and ALT high (1.6% [7 of 433 subjects] in abatacept group, 2.3% [5 of 217 subjects] in the placebo group).

On the basis of the above, the applicant explained that abatacept was shown to be effective for RA symptoms, physical functions, and structural damage to joints in RA patients who had not adequately responded to MTX, and that treatment with abatacept up to 1 year was generally well tolerated.

4.(iii).A.(2).4) Phase III study in non-Japanese RA patients who had not adequately responded to TNF-α inhibitor (5.3.5.1-5, IM101-029 [December 2002 to June 2004])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of abatacept under concomitant use of DMARD or anakinra (an IL-1 inhibitor, unapproved in Japan), in patients with active RA who had been treated with a TNF-α inhibitor for at least 3 months and were current or prior users at the time of screening, and who were considered to be poor responders[13] (target sample size of 384 subjects [256 subjects in abatacept group, 128 subjects in placebo group]).

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) or placebo was to be administered by intravenous infusion on Days 1, 15, 29, and every 28 days for up to 6 months. Washout periods of 28 and 60 days were required for current users of etanercept and infliximab, respectively. All subjects were to be concomitantly administered a fixed dose of a DMARD or anakinra throughout the study period.

A total of 391 treated subjects (258 subjects in the abatacept group, 133 subjects in the placebo group) were included in the ITT population, and subjected to the efficacy and the safety analysis.

Two primary endpoints were set for the study, and sequential comparisons were made starting from the first primary endpoint based on the closed testing procedure. The ACR 20 response at 6 months of treatment by the evaluation of RA symptoms, the first primary endpoint, is shown in Table 21. The rate was significantly higher in the abatacept group than in the placebo group. ACR 50 and 70 responses, the secondary endpoints, are also shown in Table 21.

Table 21. ACR 20, 50, and 70 responses at 6 months

	Abatacept group (256 subjects)	Placebo group (133 subjects)	Between-group difference [95% CI]	*P* value*
ACR 20 response	50.4 (129)	19.5 (26)	30.8 [20.6, 41.1]	<0.001
ACR 50 response	20.3 (52)	3.8 (5)	16.6 [8.6, 24.5]	<0.001
ACR 70 response	10.2 (26)	1.5 (2)	8.7 [2.7, 14.6]	0.003

% (number of subjects)

* Cochran-Mantel-Haenszel test using the use status (current user, prior user) of TNF-α inhibitor before treatment start as the stratification factor

The percentage of subjects who achieved clinically significant HAQ-DI (decrease of at least 0.3 points from baseline) at 6 months, in the evaluation of physical function, the second primary endpoint, was 47.3% (121 of 256 subjects) in the abatacept group and 23.3% (31 of 133 subjects) in the placebo group. Thus, the percentage was significantly higher in the abatacept group than in the placebo group ($P < 0.001$, Cochran-Mantel-Haenszel χ^2 test using the use status [current user, prior user] of TNF-α inhibitor before the start of abatacept treatment, as the stratification factor).

Adverse events (except abnormal laboratory changes) were observed in 79.5% (205 of 258 subjects) in the abatacept group and 71.4% (95 of 133 subjects) in the placebo group. Death occurred in 1 subject of the abatacept group (caused by myocardial infarction/cardiac failure

[13] Prior users and current users were, at screening and at Day 1 of administration (after washout period), respectively, confirmed to have ≥10 swollen joint counts, ≥12 tender joint counts, and CRP >1.3mg/dL.

congestive), but a causal relationship with the investigational product was ruled out. Serious adverse events were observed in 10.5% (27 of 258 subjects) in the abatacept group and 11.3% (15 of 133 subjects) in the placebo group. Those that occurred in at least 2 subjects in either group were rheumatoid arthritis (5 subjects in the abatacept group, 2 subjects in the placebo group) and cardiac failure congestive (2 subjects in the abatacept group, 1 subject in the placebo group). Adverse events, for which a causal relationship to the investigational product can not be ruled out, were observed in 2.7% (7 of 258 subjects) in the abatacept group and 0.8% (1 of 133 subjects) in the placebo group. Adverse events leading to treatment discontinuation were observed in 3.5% (9 of 258 subjects) in the abatacept group and 3.0% (4 of 133 subjects) in the placebo group. The only event observed in at least 2 subjects in either group was cardiac failure congestive (2 subjects in the abatacept group).

Adverse drug reactions were observed in 41.5% (107 of 258 subjects) in the abatacept group and 29.3% (39 of 133 subjects) in the placebo group. Those that occurred in at least 2% of subjects in either group are shown in Table 22.

Table 22. Adverse drug reactions that occurred in at least 2% of subjects in either group

	Abatacept group (N = 258)	Placebo group (N = 133)
Headache	21 (8.1)	2 (1.5)
Dizziness	9 (3.5)	2 (1.5)
Nausea	9 (3.5)	1 (0.8)
Upper respiratory tract infection	6 (2.3)	4 (3.0)
Bronchitis	6 (2.3)	3 (2.3)
Nasopharyngitis	6 (2.3)	2 (1.5)
Fatigue	3 (1.2)	4 (3.0)
Influenza	0	3 (2.3)

Number of subjects (%)

The most common abnormal laboratory changes were white blood cell count high (7.0% [18 of 258 subjects] in the abatacept group, 10.7% [14 of 133 subjects] in the placebo group) and creatinine high (4.3% [11 of 258 subjects in the abatacept group, 3.8% [5 of 133 subjects] in the placebo group).

On the basis of the above, the applicant explained that abatacept was shown to be effective for symptoms of RA and physical functions in RA patients who had not adequately responded to a TNF-α inhibitor, and that the safety profile of abatacept was acceptable.

4.(iii).A.(2).5) Study on concomitant use of abatacept with DMARDs including biological products in non-Japanese RA patients (submitted data 5.3.5.1-6, IM101-031 [December 2002 to June 2004])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted in patients with active RA with or without complications[14] (target sample size of 1333 subjects [1000 subjects in the abatacept group, 333 subjects in the placebo group]) to investigate the safety of concomitant use of abatacept with at least 1 DMARD, including biological products.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) or placebo was to be administered by intravenous infusion on Days 1, 15, 29, and every 28 days,

[14] Patients who had been treated with at least 1 DMARD including biological products for ≥3 months before treatment and showed a patient's global assessment (VAS) of ≥20 mm at screening and on Day 1 of administration. Patients with complications such as diabetes mellitus, congestive cardiac failure, or chronic obstructive pulmonary disease were considered eligible to participate in the study if their symptoms were stable.

for up to 12 months. The biological product and/or DMARD that had been administered at the time of enrollment was to be administered concomitantly at a fixed dose up to Day 85 of abatacept administration and, from Day 86 onward, dose adjustment and addition of other biological products/DMARDs were permitted. On Day 1 of administration, DMARDs, including biological products, were concomitantly used in approximately 97% of subjects in each group. MTX was the most commonly-used drug (75% to 78% of subjects). As to biological products, TNF inhibitors and anakinra were concomitantly used in approximately 9% and 2% of subjects, respectively.

A total of 1441 treated subjects (959 subjects in the abatacept group, 482 subjects in the placebo group[15]) were included in the ITT population and subjected to the efficacy and the safety analysis.

Adverse events (except abnormal laboratory changes) were observed in 90.3% (866 of 959 subjects) in the abatacept group and 86.5% (417 of 482 subjects) in the placebo group. Deaths occurred in 5 subjects in the abatacept group (hypertensive heart disease, coronary artery atherosclerosis/myocardial ischaemia, cardiac failure, cardiac arrest, sudden death) and in 4 subjects in the placebo group (myocardial infarction, cerebrovascular accident, heart-related death, *pneumocystis carinii* pneumonia). The causal relationship between *pneumocystis carinii* pneumonia and the investigational product was not ruled out. Serious adverse events were observed in 12.8% (123 of 959 subjects) in the abatacept group and 12.2% (59 of 482 subjects) in the placebo group. Those that occurred in at least 3 subjects are shown in Table 23. Serious adverse events, for which a causal relationship to the investigational product can not be ruled out, were observed in 2.4% (23 of 959 subjects) in the abatacept group and 2.7% (13 of 482 subjects) in the placebo group. The only event that occurred in at least 2 subjects in either group was pneumonia (3 subjects each in the abatacept and placebo groups). Adverse events leading to treatment discontinuation were observed in 5.4% (52 of 959 subjects) in the abatacept group and 4.1% (20 of 482 subjects) in the placebo group. Those that occurred in at least 0.3% of subjects in either group were pneumonia (0.3% [3 of 959 subjects] in the abatacept group, 0% in the placebo group), and asthenia (0.3% [3 of 959 subjects] in the abatacept group, 0% in the placebo group).

Table 23. Serious adverse events that occurred in at least 3 subjects in either group

	Abatacept group (N = 959)	Placebo group (N = 482)
Rheumatoid arthritis	31 (3.2)	19 (3.9)
Arthropathy	1 (0.1)	3 (0.6)
Pneumonia	4 (0.4)	3 (0.6)
Bronchitis	3 (0.3)	0
Basal cell carcinoma	5 (0.5)	3 (0.6)
Gastrointestinal haemorrhage	0	3 (0.6)
Chest pain	4 (0.4)	3 (0.6)
Deep vein thrombosis	3 (0.3)	1 (0.2)
Cholelithiasis	2 (0.2)	3 (0.6)

Number of subjects (%)

Adverse drug reactions were observed in 55.7% (534 of 959 subjects) in the abatacept group and 49.6% (239 of 482 subjects) in the placebo group. Those that occurred in at least 2% of subjects in either group are shown in Table 24.

[15] Subjects had been planned to be assigned to the abatacept group and the placebo group at a 3:1 ratio, but were found to have been assigned at a 2:1 ratio upon blind-breaking after the completion of the double-blind period. The number of subjects in this study had been determined based on the statistical power (87%) to detect adverse events with a 0.2% incidence in the abatacept group. The statistical power calculated based on the actual number of subjects in the abatacept group was 85%, which was judged to have no substantial impact on the analysis.

Table 24. Adverse drug reactions that occurred in at least 2% of subjects in either group

	Abatacept group (N = 959)	Placebo group (N = 482)
Headache	111 (11.6)	37 (7.7)
Nausea	60 (6.3)	30 (6.2)
Upper respiratory tract infection	57 (5.9)	27 (5.6)
Dizziness	49 (5.1)	22 (4.6)
Diarrhoea	43 (4.5)	17 (3.5)
Fatigue	41 (4.3)	14 (2.9)
Sinusitis	35 (3.6)	14 (2.9)
Nasopharyngitis	30 (3.1)	7 (1.5)
Cough	29 (3.0)	6 (1.2)
Somnolence	25 (2.6)	12 (2.5)
Urinary tract infection	25 (2.6)	8 (1.7)
Rash	23 (2.4)	9 (1.9)
Hypertension	23 (2.4)	6 (1.2)
Asthenia	20 (2.1)	6 (1.2)
Pyrexia	18 (1.9)	10 (2.1)
Vomiting	15 (1.6)	10 (2.1)
Myalgia	13 (1.4)	10 (2.1)
Oedema peripheral	9 (0.9)	10 (2.1)

Number of subjects (%)

The most common abnormal laboratory changes were white blood cell count high (7.3% [70 of 958 subjects] in the abatacept group, 11.9% [57 of 481 subjects] in the placebo group), creatinine high (4.3% [41 of 958 subjects] in the abatacept group, 6.1% [29 of 481 subjects] in the placebo group), haemoglobin low (1.3% [12 of 958 subjects] in the abatacept group, 2.9% [14 of 481 subjects] in the placebo group), white blood cell count low (2.5% [24 of 958 subjects] in the abatacept group, 2.5% [12 of 481 subjects] in the placebo group), and haematocrit low (0.9% [9 of 958 subjects] in the abatacept group, 2.5% [12 of 481 subjects] in the placebo group).

In the subgroup with concomitant use of biological products, the incidence of adverse events (95.1% [98 of 103 subjects] in the abatacept group, 89.1% [57 of 64 subjects] in the placebo group), the treatment discontinuations due to serious adverse events (4.9% [5 of 103 subjects] in the abatacept group, 3.1% [2 of 64 subjects] in the placebo group), and the incidence of serious infection (5.8% [6 of 103 subjects] in the abatacept group, 1.6% [1 of 64 subjects] in the placebo group) were higher in the abatacept group than in the placebo group.

On the basis of the above, the applicant explained that abatacept was well tolerated when concomitantly administered with DMARDs, including biological products, to patients with active RA with or without complications.

The applicant also explained that, in patients with chronic obstructive pulmonary disease, the incidence of adverse drug reactions was higher in the abatacept group (51.4% [19 of 37 subjects]) than in the placebo group (47.1% [8 of 17 subjects]), and that therefore they planned to include “patients with chronic obstructive pulmonary disease” in the “Careful Administration” section of the package insert.

4.(iii).A.(3) Long-term extension studies in Japan and foreign countries

4.(iii).A.(3).1) Phase III long-term administration study in Japanese RA patients (5.3.5.2-1.2, IM101-129 [[redacted] to ongoing (cut-off date [redacted])]

An open-label, uncontrolled study was conducted to investigate the safety and efficacy of abatacept in RA patients who had completed Study IM101-034 or IM101-071 and wished to

continue the treatment, and newly enrolled RA patients who could not be treated with MTX for safety reasons and had not adequately responded to DMARDs (other than MTX) or biological products[16] (target sample size of 180). The interim report on data obtained up to Week 48 (cut-off date [redacted] 20[redacted]) was submitted.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) was to be administered by intravenous infusion on Weeks 0, 2, 4, and every 4 weeks thereafter, until approval of abatacept. Dose adjustment of concomitant drugs including DMARDs was permitted in patients in the extended treatment group, whereas concomitant use of DMARDs was prohibited up to Week 12 in newly enrolled subject group.

A total of 217 treated subjects (13 subjects who participated in Study IM101-034, 178 subjects who participated in Study IM101-071, 26 subjects who were newly enrolled) were all included in the efficacy and the safety analysis. In all, 19 subjects discontinued the study; the main reasons included voluntary discontinuation in 9 subjects, adverse events in 5 subjects, and poor response in 5 subjects. The duration of abatacept administration (mean ± SD) throughout the entire study period, including Study IM101-034 or IM101-071, was 11.5 ± 1.7 months.

Changes over time in ACR 20, 50, and 70 responses, parameters evaluated as efficacy endpoints, are shown in Table 25.

Table 25. Changes over time in ACR 20, 50, and 70 responses

	ACR 20	ACR 50	ACR 70
Week 12	50.2% (108/215)	19.1% (41/215)	6.0% (13/215)
Week 24	62.7% (133/212)	28.3% (60/212)	11.8% (25/212)
Week 36	64.9% (135/208)	31.3% (65/208)	12.5% (26/208)
Week 48	65.7% (132/201)	40.3% (81/201)	16.4% (33/201)

Adverse events (except abnormal laboratory changes) were observed in 89.9% (195 of 217 subjects). No deaths occurred. Serious adverse events were observed in 14.3% (31 subjects). Those that occurred in at least 2 subjects were spinal compression fracture (1.4% [3 subjects]), cellulitis, femur fracture, joint destruction, and osteoarthritis (0.9% [2 subjects] each). Treatment-related serious adverse events were observed in 6.5% (14 subjects). They were cellulitis in 2 subjects, gastroenteritis, arthritis bacterial, pyrexia, acute sinusitis, osteomyelitis, sepsis/pharyngeal abscess/cerebral infarction/encephalitis, B-cell lymphoma, gastric cancer, inflammatory bowel disease, gastroenteritis viral, neuropathy peripheral, and interstitial lung disease in 1 subject each. Adverse events leading to treatment discontinuation were observed in 2.3% (5 subjects).

Adverse drug reactions (except abnormal laboratory changes) were observed in 73.3% (159 of 217 subjects). The most common adverse drug reactions were nasopharyngitis (24.9% [54 subjects]), blood pressure increased (9.2% [20 subjects]), upper respiratory tract inflammation (8.3% [18 subjects]), stomatitis (7.4% [16 subjects]), hypertension (5.1% [11 subjects]), gastroenteritis (4.1% [9 subjects]), bronchitis (3.2% ([7 subjects]), and pharyngitis (3.2% ([7 subjects]).

Abnormal laboratory changes were observed in 54.8% (119 of 217 subjects). Abnormal laboratory changes, for which a causal relationship to the treatment can not be ruled out, were observed in 39.2% (85 subjects). The most common events were lymphocyte count decreased (11.5% [25 subjects]), white blood cell count increased (10.1% [22 subjects]), ALT increased (6.5% [14 subjects]), and white blood cells urine positive (6.0% [13 subjects]).

[16] RA Patients with ≥6 swollen joint counts and ≥8 tender joint counts.

On the basis of the above, the applicant explained that administration of abatacept to Japanese RA patients for 48 weeks was well tolerated and safe and, regarding the efficacy, that improvement of RA symptoms was maintained up to Week 48.

4.(iii).A.(3).2) Phase II long-term administration study, an extension from foreign IM101-100 study (5.3.5.2-2, IM101-100LT [20 to ongoing (cut-off date 20)])

An open-label, uncontrolled study was conducted in RA patients who had completed Study IM101-100 and wished to receive continued treatment, to investigate the safety and efficacy of long-term administration of abatacept under concomitant use of MTX. An interim report (cut-off date 20) was submitted.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) was to be administered by intravenous infusion once every 30 days.[17] Adjustment of the doses of concomitant drugs (including MTX [≤30 mg/week]) and addition of 1 DMARD (except for biological products) were permitted.

A total of 219 treated subjects were included in the safety analysis. Of the subjects, 70 discontinued the study; the main reasons included adverse events (26 subjects), poor response (21 subjects), and withdrawal of consent (13 subjects). The duration of abatacept administration (mean ± SD) throughout the entire study period, including Study IM101-100, was 38.8 ± 13.8 months.

Changes over time in the ACR 20 response, an efficacy endpoint, are shown in Figure 4.

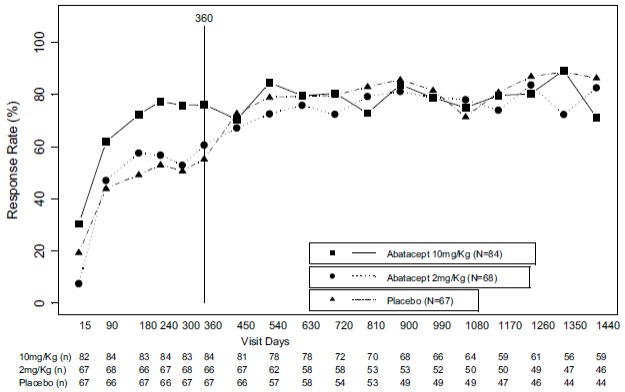


Figure 4. Change over time in ACR 20 response
(double-blind study period + long-term extension study period)

Adverse events (except abnormal laboratory changes) were observed in 95.4% (209 of 219 subjects). Deaths occurred in 3 subjects (lung adenocarcinoma with metastases to pleura, severe dyspnoea, cardiopulmonary failure), but causal relationships with the investigational product were ruled out. Serious adverse events were observed in 39.3% (86 subjects), the most common events being rheumatoid arthritis (5.0% [11 subjects]), basal cell carcinoma (1.8% [4 subjects]), osteoarthritis, dyspnoea, myocardial infarction, hip arthroplasty, and cholelithiasis (1.4% [3 subjects] each). Serious adverse events, for which a causal relationship to the investigational

[17] Of all the subjects enrolled into the study, 63 continued to receive treatment under double-blind conditions in the following manner: Subjects who had been treated with 2 mg/kg or 10 mg/kg of abatacept were administered the same dose of the drug, and those who had been treated with placebo were reassigned to placebo or abatacept (2 mg/kg) at a 1:1 ratio until the dose in the long-term study was allocated (1-5 months) after completion of 12-month treatment in Study IM101-100.

product can not be ruled out, were observed in 9.6% (21 subjects), and those observed in at least 2 subjects were arthritis bacterial, basal cell carcinoma, pleurisy, and pericarditis, each occurring in 2 subjects. Adverse events leading to treatment discontinuation were observed in 10.5% (23 subjects).

Adverse drug reactions were observed in 53.4% (117 of 219 subjects), of which those observed in at least 2% of subjects were bronchitis (6.8% [15 subjects]), nasopharyngitis (5.9% [13 subjects]), upper respiratory tract infection (5.5% [12 subjects]), sinusitis (5.0% [11 subjects]), urinary tract infection (4.1% [9 subjects]), herpes zoster (3.2% [7 subjects]), herpes simplex (2.7% [6 subjects]), rhinitis (2.3% [5 subjects]), cough (3.2% [7 subjects]), fatigue (2.3% [5 subjects]), hypertension (3.7% [8 subjects]), and headache (2.7% [6 subjects]).

The most common abnormal laboratory changes were lymphocyte count low (19.4% [42 of 217 subjects]), white blood cell count high (13.9% [30 of 216 subjects]), eosinophil count high (6.9% [15 of 217 subjects]), urea nitrogen high (6.5% [14 of 217 subjects]), haemoglobin low (6.0% [13 of 216 subjects]), ALT high (3.7% [8 of 217 subjects]), creatinine high (3.2% [7 of 217 subjects]), and haematocrit low (2.8% [6 of 216 subjects]).

4.(iii).A.(3).3) Phase II long-term administration study, an extension from foreign IM101-101 study (5.3.5.2-3, IM101-101LT [February 2002 to February 2007])

An open-label, uncontrolled study was conducted in RA patients who had completed Study IM101-101 and wished to receive continued treatment, to investigate the safety and efficacy of abatacept under concomitant use of etanercept.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) was to be administered by intravenous infusion once every 30 days for up to 4 years. Dose adjustment of concomitant drugs including etanercept and addition of 1 DMARD, as a general rule, had originally been permitted, but concomitant use of etanercept was discontinued in June 2005 in all subjects.

A total of 80 treated subjects were included in the safety analysis. Of the subjects, 50 discontinued the study; main reasons included poor efficacy in 17 subjects, withdrawal of consent in 15 subjects, and adverse events in 10 subjects. The duration of abatacept administration (mean ± SD) throughout the entire study period, including Study IM101-101, was 47.6 ± 18.2 months.

Modified ACR 20 responseson Days 360, 720, 1080, 1440, and 1800 (counted from Study IM101-101), parameters evaluated as one of the efficacy endpoints, were 65.5%, 92.3%, 84.8%, 89.7%, and 86.4%, respectively, in subjects receiving 2 mg/kg of abatacept in Study IM101-101, and 50.0%, 75.0%, 58.8%, 66.7%, and 62.5% in subjects receiving the placebo in the same study, respectively.

Adverse events (except abnormal laboratory changes) were observed in 98.8% (79 of 80 subjects). Deaths occurred in 2 subjects (diffuse large B-cell lymphoma/hepatosplenomegaly, mixed oligo-astrocytoma); causal relationships with the investigational product were not ruled out for either of them. Serious adverse events were observed in 41.3% (33 subjects), of which those observed in at least 2 subjects were rheumatoid arthritis (7.5% [6 subjects]), osteoarthritis (3.8% [3 subjects]), and atrial fibrillation (2.5% [2 subjects]). Serious adverse events, for which a causal relationship to the investigational product can not be ruled out, were observed in 7.5% (6 subjects), and were arthritis bacterial, hepatosplenomegaly, diffuse large B-cell lymphoma, pneumonia, chronic obstructive pulmonary disease, cervix carcinoma, and mixed oligo-astrocytoma in 1 subject each. Adverse events leading to treatment discontinuation occurred in 12.5% (10 subjects).

Adverse drug reactions were observed in 76.3% (61 of 80 subjects) in the abatacept group, of which those observed in at least 3% of subjects were upper respiratory tract infection (18.8% [15 subjects]), sinusitis (15.0% [12 subjects]), bronchitis (12.5% [10 subjects]), nausea (8.8% [7 subjects]), urinary tract infection and blood pressure increased (7.5% [6 subjects] each), blood pressure decreased, blood pressure diastolic decreased, and headache (6.3% [5 subjects] each), rash (5.0% [4 subjects]), pneumonia, rhinitis, abdominal discomfort, diarrhoea, fatigue, and asthma (3.8% [3 subjects] each).

The most common abnormal laboratory changes included white blood cell count high (13.8% [11 of 80 subjects]) and eosinophil count high (10.0% [8 of 80 subjects]).

4.(iii).A.(3).4) Phase III long-term study, a continuation from foreign IM101-102 study (5.3.5.2-4, IM101-102LT [20 to ongoing (cut-off date 20)])

An open-label, uncontrolled study was conducted in RA patients who had completed Study IM101-102 and wished to receive continued treatment, to investigate the safety and efficacy of long-term abatacept administration. An interim report with the cut-off date of 20 was submitted.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) was to be administered by intravenous infusion once every 28 days. Dose adjustments of DMARDs and other concomitant drugs were permitted.

A total of 539 treated subjects were included in the safety analysis. Of the subjects, 51 discontinued the study; the main reasons included adverse events in 19 subjects, withdrawal of consent in 12 subjects, and poor response in 11 subjects. The duration of abatacept administration (mean ± SD) throughout the entire study period, including Study IM101-102, was 22.7 ± 6.1 months.

The ACR 20 responses on Days 365, 449, 533, 617, and 729 (counted from Study IM101-102), parameters evaluated as one of the efficacy endpoints, were 81.9%, 81.1%, 80.9%, 81.6%, and 80.3%, respectively, in subjects receiving abatacept in Study IM101-102, and 53.8%, 77.5%, 81.3%, 80.0%, and 78.1% in subjects receiving placebo, in the same study.

Adverse events (except abnormal laboratory changes) were observed in 87.2% (470 of 539 subjects). Deaths occurred in 2 subjects (lobar pneumonia, myocardial ischaemia/post procedural complication); a causal relationship with the investigational product was not ruled out for lobar pneumonia. Serious adverse events were observed in 17.8% (96 subjects), of which those observed in at least 2 subjects were rheumatoid arthritis (3.5% [19 subjects]), osteoarthritis (1.5% [8 subjects]), bronchitis acute and chest pain (0.6% [3 subjects] each), cellulitis, lobar pneumonia, pneumonia, postoperative infection, basal cell carcinoma, uterine leiomyoma, post procedural complication, transient ischaemic attack, breast mass, and anaemia (0.4% [2 subjects] each). Serious adverse events, for which a causal relationship to the investigational product can not be ruled out, were observed in 4.8% (26 subjects). Of the events, those observed in at least 2 subjects were lobar pneumonia and postoperative infection (2 subjects each). Adverse events leading to treatment discontinuation occurred in 3.7% (20 subjects).

Adverse drug reactions were observed in 36.9% (199 of 539 subjects), of which those observed in at least 2% of subjects were upper respiratory tract infection (5.0% [27 subjects]), nasopharyngitis (3.5% [19 subjects]), urinary tract infection (3.2% [17 subjects]), bronchitis (2.0% [11 subjects]), diarrhoea (2.2% [12 subjects]), and headache (2.4% [13 subjects]).

The most common abnormal laboratory changes were creatinine high (11.0% [59 of 536 subjects]), white blood cell count high (7.5% [40 of 536 subjects]), and white blood cell count low (3.4% [18 of 536 subjects]).

4.(iii).A.(3).5) Long-term administration study, an extension from foreign IM101-029 study (5.3.5.2-5: IM101-029LT [[redacted] to ongoing (cut-off date [redacted])])

An open-label, uncontrolled study was conducted in RA patients who had completed Study IM101-029 and wished to receive continued treatment, to investigate the safety and efficacy of long-term abatacept administration under concomitant use of DMARD or anakinra. An interim report with the cut-off date of [redacted] was submitted.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) was to be administered by intravenous infusion once every 28 days. Dose adjustment of concomitant drugs, including DMARDs and anakinra, was permitted.

A total of 317 treated subjects were included in the analyses of safety and efficacy. Of the subjects, 74 discontinued the study; main reasons included poor response in 42 subjects and adverse events in 18 subjects. The duration of abatacept administration (mean ± SD) throughout the entire study period, including Study IM101-029, was 19.4 ± 5.7 months.

The ACR 20 responses on Days 169, 365, 449, and 533 (counted from Study IM101-029), one of the parameters evaluated as efficacy endpoints, were 59.4%, 59.9%, 58.5%, and 56.7%, respectively, in subjects receiving abatacept in Study IM101-029, and 26.3%, 63.6%, 63.6%, and 59.6%, respectively, in subjects receiving the placebo in the same study.

Adverse events (except abnormal laboratory changes) were observed in 90.5% (287 of 317 subjects). Death occurred in 1 subject (respiratory failure); a causal relationship with the investigational product was not ruled out. (Death caused by bile duct cancer was also observed in 1 subject not earlier than 56 days after the last dose in Study IM101-029.) Serious adverse events were observed in 26.5% (84 of 317 subjects), of which those observed in at least 3 subjects were rheumatoid arthritis (7.3% [23 subjects]), osteoarthritis, and pneumonia (1.9% [6 subjects] each), arthritis, lobar pneumonia, hip fracture, chest pain, and obesity (0.9% [3 subjects] each). Serious adverse events, for which a causal relationship to the investigational product can not be ruled out, were observed in 4.4% (14 subjects). Of the events, the only one observed in at least 2 subjects was pneumonia (1.6% [5 subjects]). Adverse events leading to treatment discontinuation occurred in 5.0% (16 subjects).

Adverse drug reactions (except abnormal laboratory changes) were observed in 45.1% (143 of 317 subjects), of which those observed in at least 2% of subjects were upper respiratory tract infection (8.2% [26 subjects]), headache (6.0% [19 subjects]), sinusitis (5.0% [16 subjects]), bronchitis (4.4% [14 subjects]), urinary tract infection (4.4% [14 subjects]), nasopharyngitis (4.1% [13 subjects]), dizziness (3.5% [11 subjects]), nausea, and fatigue (2.5% [8 subjects] each).

The most common abnormal laboratory changes were serum creatinine high (13.0% [41 of 315 subjects]), white blood cell count high (12.4% [39 of 315 subjects]), AST high (2.5% [8 of 315 subjects]), ALT high (2.2% [7 of 315 subjects]), and haematocrit low (2.2% [7 of 315 subjects]).

4.(iii).A.(3).6) Long-term administration study, an extension from foreign IM101-031 study (5.3.5.2-6: IM101-031LT [[redacted] to ongoing (cut-off date [redacted])])

An open-label, uncontrolled study was conducted in RA patients who had completed Study IM101-031 and wished to receive continued treatment, to investigate the safety of long-term

abatacept administration under concomitant use of DMARDs, including biological products. An interim report with the cut-off date of [redacted] was submitted.

Abatacept (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [≥100 kg]) was to be administered by intravenous infusion once every 28 days. Dose adjustments of concomitant drugs, including DMARDs and biological products, were permitted.

A total of 1184 subjects were included in the safety analysis. Of the subjects, 113 discontinued the study; main reasons included adverse events in 39 subjects, withdrawal of consent in 30 subjects, and poor response in 29 subjects. The duration of abatacept administration (mean ± SD) throughout the entire study period, including Study IM101-031, was 21.5 ± 6.2 months.

Adverse events (except abnormal laboratory changes) were observed in 86.0% (1018 of 1184 subjects). Deaths occurred in 6 subjects (cardiac arrest, small cell lung cancer, victim of homicide, septic shock, cardiac failure congestive/suture related complication, gastric cancer); causal relationships with the investigational product were not ruled out for septic shock and gastric cancer (deaths occurred in an additional 4 subjects not earlier than 56 days after the last dose [cholelithiasis, cerebrovascular accident, death, leukopenia/death]; a causal relationship with the investigational product was not ruled out for leukopenia/death). Serious adverse events were observed in 14.6% (173 of 1184 subjects), of which those observed in at least 3 subjects were rheumatoid arthritis (1.9% [23 subjects]), osteoarthritis (0.6% [7 subjects]), abdominal pain (0.4% [5 subjects]), arthritis, synovitis, and pneumonia (0.3% [4 subjects] each), diverticulitis, pyelonephritis acute, urinary tract infection, dyspepsia, myocardial infarction, transient ischaemic attack, cholecystitis, cholelithiasis, and chest pain (0.3% [3 subjects] each). Serious adverse events, for which a causal relationship to the investigational product can not be ruled out, were observed in 3.6% (43 subjects). Of the events, those observed in at least 2 subjects were pneumonia (0.3% [3 subjects]), pyelonephritis acute and overdose (0.2% [2 subjects] each). Adverse events leading to treatment discontinuation occurred in 3.2% (38 subjects).

Adverse drug reactions (except abnormal laboratory changes) were observed in 41.2% (488 of 1184 subjects), of which those observed in at least 2% of subjects were upper respiratory tract infection (5.9% [70 subjects]), bronchitis (3.4% [40 subjects]), headache (3.0% [36 subjects]), nasopharyngitis, and sinusitis (2.4% [28 subjects] each), dizziness (2.3% [27 subjects]), and hypertension (2.2% [26 subjects]).

The most common abnormal laboratory changes were white blood cell count high (7.6% [90 of 1184 subjects]), serum creatinine high (7.1% [84 of 1183 subjects]), white blood cell count low (3.8% [45 of 1184 subjects]), and ALT high (2.1% [25 of 1183 subjects]).

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Ability to extrapolate foreign clinical study data

PMDA asked the applicant to explain the possibility that the difference in baseline patient characteristics may have affected the efficacy evaluation, given the higher efficacy (ACR 20 response at 6 months of treatment) in the abatacept 2 and 10 mg/kg groups in the Japanese IM101-071 study as compared with the foreign IM101-100 study.

The applicant explained as follows:
The MTX dose before starting abatacept administration was obviously lower in the Japanese study than in the foreign study, reflecting the difference in the approved dose of MTX (foreign countries, 15-16 mg/week; Japan, 7 mg/week [mean value, same hereafter]). Comparison of baseline RA conditions showed no substantial difference in disease duration, physical function,

or CRP, whereas the tender joint counts (foreign countries, 28.2-30.8; Japan, 21.0-21.8) and the swollen joint counts (foreign countries, 20.2-21.8; Japan, 16.6-17.6) were both slightly lower in the Japanese study. The possibility that these differences might somehow have affected the observed difference in efficacy cannot be excluded. However, when the ACR 20 response in the foreign study was included in the subgroup analysis stratified by MTX dose (<15 mg/week, ≥15 mg/week), there was no substantial difference between the subgroups, 58.7% (27 of 46 subjects) vs. 62.3% (43 of 69 subjects) in the 10 mg/kg group, 44.4% (16 of 36 subjects) vs. 40.6% (28 of 69 subjects) in the 2 mg/kg group, and 27.0% (10 of 37 subjects) vs. 39.0% (32 of 82 subjects) in the placebo group (subgroup analysis was not performed in the Japanese study because of the narrow dose range of MTX, 6-8 mg/week). In addition, the subgroup analysis of the Japanese study stratified by the tender joint counts showed that the ACR 20 response tended to be slightly higher in the group with ≤15 tender joint counts than in the group with ≥25 tender joint counts, whereas subgroup analysis stratified by the swollen joint counts showed no substantial difference in ACR 20 responses between the subgroups in either study. These results suggest that there were no differences between the 2 studies in baseline patient characteristics that might have substantially affected the efficacy, and therefore there should be no major problems in extrapolating the foreign clinical data to Japanese patients.

PMDA considers as follows:
In the Japanese study, the studied patients used a lower dose of MTX and had lower tender and swollen joint counts than patients in the foreign study. However, these differences are unlikely to substantially affect the efficacy of abatacept, judging from the submitted data, the applicant's responses to the inquiries, etc. In addition, although ACR 20 responses differed, the dose-response relationship was similar, suggesting that there is no essential difference between the Japanese and the foreign clinical studies. By also taking into account the fact that bridging has generally been demonstrated to be possible for related drugs in the field of RA, PMDA has concluded that foreign clinical data of abatacept can be extrapolated to Japanese RA patients.

4.(iii).B.(2) Efficacy and clinical positioning
4.(iii).B.(2).1) Clinical positioning
PMDA asked the applicant to explain their views on the clinical positioning of abatacept relative to other biological products that have already been approved for RA therapy in Japan.

The applicant explained as follows:
a. Table 26 shows ACR responses achieved by abatacept and by approved biological products (TNF inhibitors infliximab, adalimumab, and etanercept; and the IL-6 inhibitor tocilizumab) in dose-response studies conducted in Japan. These data show that efficacy does not differ substantially among drugs although careful interpretation of the data is required because of the differences in the dosage regimen, treatment duration, use or non-use of concomitant MTX, subject inclusion criteria, etc., among clinical studies.

b. In a foreign randomized, double-blind, placebo-controlled comparative study to evaluate the efficacy and safety of abatacept (fixed dose of approximately 10 mg/kg calculated based on body weight) and infliximab (3 mg/kg) in active RA patients who had not adequately responded to MTX (Study IM101-043), the incidences of serious adverse events after 1 year of administration (9.6% [15 of 156 subjects] in the abatacept group, 18.2% [30 of 165 subjects] in the infliximab group), serious infection (1.9% [3 of 156 subjects] in the abatacept group, 8.5% [14 of 165 subjects] in the infliximab group), etc., were slightly lower in the abatacept group than in the infliximab group, and there was no tendency for any particular adverse events occurring more frequently in the abatacept group. As regarding efficacy, though the data were obtained by post-hoc analysis, the ACR 20 response at 6 months of treatment was 66.7% in the abatacept group, 59.4% in the infliximab group, and 41.8% in the placebo group, showing

similar results in the abatacept and infliximab groups. These results suggest that abatacept may be used as one of the first-line drugs for RA patients who have not adequately responded to existing anti-rheumatic agents, with at least equivalent clinical positioning to the existing biological products.

Table 26. Comparison of efficacy between abatacept and approved biological products in Japanese studies

Drug	Abatacept			Infliximab			Etanercept		
Study (period)	IM101-071 (6 months)			TA-650-P3-01 (14 weeks)			202-JA (3 months)		
Concomitant drug	MTX			MTX			None		
Treatment group	Placebo (N = 66)	2 mg/kg (N = 67)	10 mg/kg (N = 61)	Placebo (N = 47)	3 mg/kg (N = 49)	10 mg/kg (N = 51)	Placebo (N = 48)	10 mg (N = 50)	25 mg (N = 49)
ACR 20	21.2 (14)	62.7 (42)	77.0 (47)	23.4 (11)	61.2 (30)	52.9 (27)	6.3 (3)	64.0 (32)	65.3 (32)
ACR 50	6.1 (4)	37.3 (25)	45.9 (28)	8.5 (4)	30.6 (15)	35.3 (18)	0 (0)	32.0 (16)	26.5 (13)
ACR 70	0 (0)	16.4 (11)	21.3 (13)	-	-	-	0 (0)	12.0 (6)	10.2 (5)

Drug	Adalimumab			Tocilizumab		
Study (period)	M02-575 (6 months)			MRA009JP (3 months)		
Concomitant drug	None			None		
Treatment group	Placebo (N = 87)	40 mg/kg (N = 91)	80 mg/kg (N = 87)	Placebo (N = 53)	4 mg/kg (N = 54)	8 mg/kg (N = 55)
ACR 20	13.8 (12)	44.0 (40)	50.6 (44)	11.3 (6)	57.4 (31)	78.2 (43)
ACR 50	5.7 (5)	24.2 (22)	32.2 (28)	1.9 (1)	25.9 (14)	40.0 (22)
ACR 70	1.1 (1)	12.1 (11)	14.9 (13)	0 (0)	20.4 (11)	16.4 (9)

% (number of subjects)

Recommended dose of abatacept. Other drugs were used at the approved doses.

The applicant also provided the following explanation:
TNF inhibitors and IL-6 inhibitors target cytokines or their receptors, whereas abatacept acts on T cells via CD28 co-stimulatory signals, thereby down-regulating the productions of cytokines such as TNF-α, IL-2, and IFN-γ. Thus, abatacept acts by a mechanism different from that of the existing drugs. The foreign study IM101-029 showed abatacept to be effective even in active RA patients who had not adequately responded to TNF inhibitors (etanercept and/or infliximab), which suggests that abatacept is a useful therapeutic agent for RA patients who have not adequately responded to existing biological products.

PMDA considers as follows:
Given the efficacy and safety profiles of abatacept that are currently available, there is no particular problem in positioning abatacept as a biological product for RA patients who have not adequately responded to existing anti-rheumatic agents, as is the case with other biological products for RA treatment. However, since use experiences of abatacept in Japan and elsewhere are insufficient, it will be necessary to further clarify the characteristics and the clinical positioning of the product by accumulating a sufficiently large volume of safety information in

the future. Abatacept acts by a novel mechanism and, in foreign studies, was shown to be effective in patients unresponsive to TNF inhibitors, raising an expectation that the product may also be useful in patients unresponsive to other biological products. However, no similar data have been obtained in Japan, nor are there efficacy data in patients unresponsive to IL-6 inhibitors in either Japan or foreign countries. Therefore, these points should be investigated in the post-marketing surveillance, and results be provided appropriately to medical practice. In addition, it is assumed that other biological products may be used for patients unresponsive to abatacept, but there are currently no pertinent data in either Japan or other countries. Such data will be important in choosing biological products to be used, and therefore need to be investigated in future.

4.(iii).B.(2).2) Efficacy and safety of abatacept monotherapy

Most clinical studies on abatacept were conducted under concomitant use of a DMARD (mainly MTX). PMDA asked the applicant to discuss the efficacy and safety of abatacept monotherapy as compared with those of combination therapy with MTX, etc., since abatacept is expected to be also used alone in patients who cannot be treated with MTX, etc., for safety reasons.

The applicant explained as follows:

Since there are no studies that directly compared abatacept monotherapy and combination therapy with MTX, it is difficult to accurately evaluate the risks and benefits of each dosage regimen. However, comparison of the following 2 foreign clinical studies has been conducted: (1) Study IM103-002 which investigated, in an exploratory manner, the efficacy and safety of abatacept monotherapy in active RA patients who had not adequately responded to at least 1 DMARD or etanercept, and (2) Study IM101-100 which investigated the efficacy and safety of abatacept under concomitant use of MTX in active RA patients who had not adequately responded to MTX. ACR 20, 50, and 70 responses at 3 months of treatment in the 10 mg/kg group are shown in Table 27. ACR 50 and 70 responses were slightly higher under concomitant use of MTX, whereas the ACR 20 response was comparable between the 2 studies. As regarding safety, the incidence of adverse events was comparable between the 2 studies, and the incidence of adverse events classified by system organ class (SOC) showed no distinct tendency unique to either study, which suggests that there are no significant differences in safety profiles between the 2 studies. Furthermore, there are no data suggestive of differences in the percentage of patients with antibody production in the presence or absence of concomitant MTX. These results suggest the usefulness of abatacept monotherapy in patients intolerant to DMARDs. In addition, the Japanese long-term study (IM101-129) which investigated the efficacy and safety of abatacept monotherapy included some patients who could not be treated with MTX for safety reasons and had not adequately responded to DMARDs other than MTX or biological products. When ACR 20, 50 and 70 responses at12 weeks of treatment were compared between these subjects and those who were treated under concomitant use of DMARDs including MTX continuously from the preceding study, the rates were 58.3% (14 of 24 subjects), 29.2% (7 of 24 subjects), and 8.3% (2 of 24 subjects), respectively, in the abatacept monotherapy group and 49.2% (94 of 191 subjects), 17.8% (34 of 191 subjects), and 5.8% (11 of 191 subjects), respectively, in the DMARD combination use group. As regards safety, the incidence of serious adverse events up to 48 weeks of treatment tended to be higher in the abatacept monotherapy group (30.8% [8 of 26 subjects]) than in the DMARD combination use group (12.0% [23 of 191 subjects]), but the types of observed adverse events did not differ significantly between the 2 groups, and all resolved or were resolving, suggesting that abatacept monotherapy was well tolerated.

Table 27. Comparison of ACR responses at 3 months in Studies IM103-002 and IM101-100

		Study IM103-002 (Abatacept monotherapy)		Study IM101-100 (MTX combination use)	
		Abatacept 10 mg/kg group (N = 32)	Placebo group (N = 32)	Abatacept 10 mg/kg group (N = 115)	Placebo group (N = 119)
ACR 20 response	% (Number of subjects)	53.1 (17)	31.3 (10)	53.9 (62)	35.3 (42)
	Between-group difference in response (%)[a]	21.9 (-1.7, 45.5)		18.6 (5.9, 31.4)	
	P value	NA		0.004	
ACR 50 response	% (Number of subjects)	15.6 (5)	6.3 (2)	24.3 (28)	12.6 (15)
	Between-group difference in response (%)[a]	9.4 (-5.7, 24.5)		11.7 (18, 21.7)	
	P value	NA		0.02	
ACR 70 response	% (Number of subjects)	6.3 (2)	0	8.7 (10)	0.8 (1)
	Between-group difference in response (%)[a]	6.3 (-2.1, 14.6)		7.9 (2.4, 13.3)	
	P value	NA		0.005	

a: point estimate (95% CI)

PMDA considers as follows:
Judging from the above explanation, abatacept monotherapy is expected to be useful in patients intolerant to MTX, etc. However, since data supporting this speculation are limited, it is necessary to continue careful investigation of the efficacy and safety of abatacept monotherapy in such patients in the post-marketing surveillance and to provide the information obtained to medical practice. Also, it is appropriate to provide cautions in the package insert that use experience with abatacept monotherapy is limited.

4.(iii).B.(2).3) Suppression of structural damage to joints

PMDA considers as follows:
Judging from the clinical study data submitted, the efficacy of abatacept in improving symptoms such as arthralgia in Japanese RA patients has been demonstrated. On the other hand, the suppressive effect against structural damage to joints has not been investigated in Japanese patients although the efficacy was confirmed in foreign patients. Given that the suppressive effect against structural damage to joints does not necessarily correlate with the symptom-improving effect, it is difficult to appropriately evaluate the suppressive effect in Japanese patients based on the results obtained from foreign patients, and it is of clinical significance to investigate the suppressive effect under actual use conditions in Japan because suppressing structural damage to joints is one of the ultimate goals of RA therapy, along with improving symptoms. In addition, such investigation will provide important data for the accurate positioning of abatacept among biological products. Therefore, the suppressive effect against structural damage to joints should be evaluated in post-marketing clinical studies after approval.

4.(iii).B.(3) Dosage and administration

4.(iii).B.(3).1) Usefulness of the dose of 2 mg/kg

PMDA asked the applicant to explain the views on the necessity of including 2 mg/kg among the clinical doses of abatacept for Japanese RA patients, in light of the findings that significant improvement effects, such as increased ACR responses, were observed not only in the 10 mg/kg group but also in the 2 mg/kg group, in the Japanese study IM101-071.

The applicant explained as follows:
a. In the Japanese study IM101-071, the ACR 20 response at 6 months of treatment, the primary endpoint, was significantly higher in the 2 mg/kg group (62.7%) than in the placebo group

(21.2%), but the rate was much higher in the 10 mg/kg group, at 77.0%, and therefore the dose-response observed was similar to that in the foreign study IM101-100.

b. In the Japanese study IM101-071, ACR 50 and 70 responses, DAS28, and HAQ at 6 months of treatment, the secondary endpoints, improved significantly in the 2 mg/kg group as compared with the placebo group. However, the response rate in the 10 mg/kg group was consistently higher than that in the 2 mg/kg group for all parameters, as shown in Table 28.

c. In subjects in the 2 mg/kg group who proceeded to the long-term administration study IM101-129, ACR responses tended to increase after increasing the dose to 10 mg/kg (ACR 20, 50, and 70 responses at 6 months of treatment were 81.0% [51 of 63 subjects], 50.8% [32 of 63 subjects], and 25.4% [16 of 63 subjects], respectively).

d. In Study IM101-071, the incidence of subjective/objective findings regarded as adverse events was 72.1% in the 10 mg/kg group and 73.1% in the 2 mg/kg group, and the incidence of adverse drug reactions was 49.2% in the 10 mg/kg group and 59.7% in the 2 mg/kg group. The incidence of serious adverse events was slightly higher in the 10 mg/kg group (8.2%) than in the 2 mg/kg (3.0%), but no serious adverse events leading to treatment discontinuation or death occurred in either group.

These results suggest that the safety profiles are comparable between the 10 mg/kg and 2 mg/kg groups. Thus, the dose of 2 mg/kg is not clearly superior to 10 mg/kg in safety, but tends to be inferior to 10 mg/kg in efficacy. Therefore, 10 mg/kg is more appropriate as the recommended dose for Japanese patients; it is expected to be beneficial in a greater number of patients.

Table 28. ACR responses, summary of DAS28 (CRP), and HAQ improvement rate at 6 months of treatment in Study IM101-071

		Abatacept group		Placebo group (N = 66)
		10 mg/kg (N = 61)	2 mg/kg (N = 67)	
ACR 20 response	Number (%) of subjects	47 (77.0)	42 (62.7)	14 (21.2)
	Difference in response rate (%) from placebo group[a]	55.8 (41.4, 70.3)	41.5 (26.3, 56.7)	N/A
	P value (vs. placebo group)	<0.001	<0.001	N/A
ACR 50 response	Number (%) of subjects achieving improvement	28 (45.9)	25 (37.3)	4 (6.1)
	Difference in response rate (%) from placebo group[a]	39.8 (26.1, 53.6)	31.3 (18.3, 44.2)	N/A
	P value (vs. placebo group)	<0.001	<0.001	N/A
ACR 70 response	Number (%) of subjects	13 (21.3)	11 (16.4)	0
	Difference in response rate (%) from placebo group[a]	21.3 (11.0, 31.6)	16.4 (7.5, 25.3)	N/A
	P value (vs. placebo group)	<0.001	0.002	N/A
DAS28 (CRP)	Number (%) of subjects achieving clinically significant improvement (decrease in DAS28 by ≥1.2)	54 (88.5)	46 (68.7)	20 (30.3)
HAQ improvement rate	Number (%) of subjects	37 (60.7)	33 (49.3)	16 (24.2)
	Difference in improvement rate (%) from placebo group	36.4 (20.4, 52.5)	25.0 (9.2, 40.8)	N/A

a: point estimate (95% CI); NA, not applicable

PMDA considers as follows:
The dose of 2 mg/kg is inferior to 10 mg/kg in the risk-benefit balance, as explained by the applicant. In addition, Study IM101-071 showed that the mean serum trough concentration in the 2 mg/kg group to be 4 to 7 μg/mL. The value is lower than that of the 10 μg/mL dose, which is the level expected to provide maximum clinical effect in most patients. In light of these facts,

it is appropriate to select only the fixed dose of approximately 10 mg/kg calculated based on body weight as the recommended dose for Japanese patients, instead of including 2 mg/kg among the recommended doses. On the other hand, given the dose response difference between abatacept 2 mg/kg and 10 mg/kg, a dose lower than 10 mg/kg may be effective in some patients. In addition, it is expected that lower doses will be attempted in elderly patients at medical practice. Therefore, it will be appropriate to ascertain the doses of abatacept actually used in the post-marketing surveillance, to evaluate both efficacy and safety in patients treated with lower doses, and to provide information to medical practice.

4.(iii).B.(3).2) Appropriateness of fixed doses based on body weight

PMDA asked the applicant to explain the appropriateness of using the fixed doses (500 mg [body weight <60 kg], 750 mg [60 to 100 kg], 1000 mg [>100 kg]) instead of dose per body weight, by providing the expected body weight range of RA patients in Japan and the range of the estimated serum trough concentration in each body weight group. PMDA also asked the applicant to explain the measures to be taken for patients with body weights being substantially outside the above range.

The applicant explained as follows:

According to the body weight range of Japanese RA patients enrolled in the Japanese phase II study (IM101-071) or the long-term extension study (IM101-129), the body weights of most RA patients in Japan are expected to be within the range of 35 to 90 kg. This body weight range was stratified in 10-kg increments and, using the parameters obtained by PPK analysis of Japanese RA patients, distribution of the estimated trough concentrations in each stratum following the administration of the fixed dose based on body weight was calculated and compared among the body weight strata. Results showed that the distribution range of the trough concentration was slightly large in the 30 to 40 kg and 60 to 70 kg strata where the patients receive a relatively higher dose per body weight of abatacept, but 84% of all patients showed a trough concentration of at least 10 μg/mL, the level expected to provide the maximum clinical efficacy. In addition, the trough concentration of the 40 to 60 kg stratum, which includes the largest percentage of patients, encompassed most of the trough concentrations in the other body weight strata. The median (range) of the observed trough concentrations in the 10 mg/kg group in Study IM101-071 was 20 (4-55) μg/mL, which was comparable to the trough concentration of 24 (3-67) μg/mL observed at the fixed dose based on body weight in Study IM101-129. These results suggest that the efficacy achieved by administering abatacept at the fixed dose based on body weight is similar to that obtained at 10 mg/kg. Therefore, it is appropriate to use fixed doses based on body weight.

The applicant also explained as follows:

Regarding patients in whom abatacept was administered at a dose exceeding 10 ± 2.5 mg/kg (those with body weight of <40 kg), the phase I study in Japanese RA patients has shown that the drug is well tolerated up to 16 mg/kg (corresponding to the 500 mg dose administered to a patient with a body weight of approximately 31 kg). In addition, the long-term extension study included 3 patients with body weights of <40 kg, and the efficacy and safety in these patients were similar to those in other body weight strata. There are no experiences in Japanese studies where abatacept was administered at doses lower than 10 ± 2.5 mg/kg (those with body weight of ≥133 kg). However, according to the analysis of the results of foreign phase III studies (IM101-102, 029, 031) involving non-Japanese RA patients, with stratification of body weight range (33-160 kg) of all patients in 10-kg increments, no clear difference was observed among strata in any of the parameters measured: the ACR 20 response, HAQ score, incidence of serious adverse events, and incidence of adverse events classified by SOC. Therefore, no particular measures are planned for patients deviating from the above range.

PMDA accepted the above response. However, since it is expected that there are a substantial number of patients in particular elderly female RA patients with body weights of <40 kg, it is necessary to investigate in further detail the safety and efficacy in patients with body weights deviating from the pre-set range, particularly in those with body weights of <40 kg, in the post-marketing surveillance, etc., because of the limited data currently available on the use of abatacept in these patients.

4.(iii).B.(4) Safety

Adverse events observed in foreign pivotal clinical studies on abatacept (IM101-100, 101, 102, 029, 031), their long-term extension studies, and Japanese clinical studies are summarized in Tables 29 and 30.

Table 29. Adverse events in foreign pivotal studies and their long-term extension studies

	Foreign pivotal studies		Long-term extension studies
	Abatacept group (N = 1955)	Placebo group (N = 989)	Abatacept (N = 2340)
Death	9 (0.5)	7 (0.7)	42 (1.8)
Serious adverse events	273 (14.0)	124 (12.5)	843 (36.0)
Serious adverse events leading to treatment discontinuation	55 (2.8)	16 (1.6)	139 (5.9)
Treatment-related serious adverse events	61 (3.1)	17 (1.7)	225 (9.6)
All adverse events	1737 (88.8)	842 (85.1)	2225 (95.1)
Adverse events leading to treatment discontinuation	113 (5.8)	39 (3.9)	209 (8.9)
Treatment-related adverse events	1020 (52.2)	456 (46.1)	1389 (59.4)

Number of subjects (%)

Table 30. Adverse events in Japanese clinical studies

	Study IM101-071 (6 months)			Study IM101-129 (1 year)
	Abatacept group		Placebo group (N = 66)	Abatacept Fixed dose based on body weight (N = 217)
	10 mg/kg (N = 61)	2 mg/kg (N = 67)		
Death due to subjective/objective adverse events	0	0	0	0
Serious subjective/objective adverse events	5 (8.2)	2 (3.0)	6 (9.1)	31 (14.3)
Serious subjective/objective adverse events leading to treatment discontinuation	0	0	2 (3.0)	5 (2.3)
Treatment-related serious subjective/objective adverse events	2 (3.3)	0	1 (1.5)	14 (6.5)
All subjective/objective adverse events	44 (72.1)	49 (73.1)	41 (62.1)	195 (89.9)
Subjective/objective adverse events leading to treatment discontinuation	0	0	2 (3.0)	5 (2.3)
Treatment-related subjective/objective adverse events	30 (49.2)	40 (59.7)	23 (34.8)	159 (73.3)

Number of subjects (%)

In the foreign pivotal studies, the number of deaths was similar in the abatacept group and the placebo group, with most deaths being caused by cardiovascular diseases. The incidence of serious adverse events was slightly higher in the abatacept group. However, the incidences of the most common serious adverse events, such as rheumatoid arthritis, pneumonia, chest pain, basal cell carcinoma, osteoarthritis, and cardiac failure congestive, were similar in the 2 treatment groups. Among all adverse events, those that occurred ≥2% more frequently in the abatacept group than in the placebo group were headache, nasopharyngitis, dizziness, dyspepsia, and hypertension. Causes of deaths in the long-term extension studies were similar to those observed in the pivotal studies. The causes included cardiovascular diseases in 17 subjects, malignant tumors in 11 subjects, and infections in 7 subjects. Similarly to the cases in the pivotal studies, a majority of serious adverse events were classified by SOC as "musculoskeletal

and connective tissue disorders," "infections and infestations," "neoplasms benign, malignant and unspecified," or "cardiac disorders."

In the Japanese clinical studies, no deaths occurred, nor was there any increasing tendency in the incidence of serious adverse events in the abatacept group as compared with the placebo group. In the phase II study (IM101-071), "infections and infestations" and "gastrointestinal disorders" occurred with high incidences. Similar tendencies were observed in the long-term extension study (IM101-129).

4.(iii).B.(4).1) Differences in safety profiles between abatacept and existing biological products

PMDA asked the applicant to explain the tendencies for the occurrences of abatacept-induced significant adverse events that should be considered when treating RA with approved biological products (e.g., serious infections, tuberculosis, serious allergic reactions, interstitial pneumonia, autoimmune disease [lupus-like syndrome, etc.], demyelinating disease, cytopenia, cardiac failure, malignant tumor) by referring to the incidences of adverse events with drugs of the same class, and to explain whether or not adequate cautions are provided in the currently proposed package insert.

The applicant explained as follows, based on the data of Japanese and foreign clinical studies and post-marketing surveillances on abatacept, infliximab, etanercept, adalimumab, and tocilizumab, and by comparing the incidence of each event:

The applicant's response is based on the following data. Data on abatacept were derived from Japanese clinical studies (Studies IM101-071 and IM101-129 [cut-off date [redacted] 20[redacted]]), pooled analysis of foreign pivotal studies (Studies IM101-100, 101, 102, 029, 031) (1955 subjects in the abatacept group, 989 subjects in the placebo group), cumulative data in foreign countries (4149 subjects), and foreign post-marketing safety reports (spontaneous reports collected from December 23, 2005 [international birth date] to December 22, 2008 and post-marketing phase IV clinical studies, including results of phase I to III studies accumulated during the same period for serious allergic reactions, lupus-like syndrome, systemic lupus erythematosus, psoriasis). Data on approved biological products were derived from the following publicly available information: Review Reports and Japanese post-marketing all-case surveillances, (infliximab, Japanese post-marketing all-case surveillance as of February 2006 [7678 RA patients]; etanercept, published report on all-case surveillance [Post-marketing Surveillance of the Safety and Effectiveness of Etanercept in Japan, *Journal of Rheumatology* 2009, 36 (5), 898-906]; adalimumab, early post-marketing phase vigilance as of November 2009 [1531 RA patients]; and tocilizumab, post-marketing all-case surveillance as of November 2009 [8509 RA patients]).

(a) Infection

i) Serious infection

Incidence of serious infections and the most common serious adverse events in Japanese and foreign clinical studies and foreign post-marketing safety reports on abatacept are shown in Table 31.

Table 31. Serious infections in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008)*
	Study IM101-071		Long-term extension study	Double-blind comparative study		Cumulative data	Estimated number of exposed patients 32,187 person-years†
	Abatacept N = 128	Placebo N = 66	Abatacept N = 217	Abatacept N = 1955	Placebo N = 989	Abatacept N = 4149	
Serious infection	1 (0.8%)	0	8 (3.7%)	58 (3.0%)	19 (1.9%)	320 (7.7%)	125 events
Most common events	Parvovirus infection	0	Cellulitis (2 subjects) Acute sinusitis Gastroenteritis Gastroenteritis viral Osteomyelitis Sepsis Arthritis bacterial Pharyngeal pustule (1 subject each)	Pneumonia (0.5%) Cellulitis (0.3%) Urinary tract infection Bronchitis Diverticulitis Localised infection Pyelonephritis acute (0.2% each)	Pneumonia (0.5%) Sepsis (0.3%) Cellulitis (0.2%)	Pneumonia (1.3%) Urinary tract infection (0.5%) Cellulitis (0.5%) Bronchitis Diverticulitis (0.4% each) Gastroenteritis Lobar pneumonia Pyelonephritis acute (0.3% each)	Pneumonia (24 events) Sepsis (14 events) Bronchitis Herpes zoster Pyelonephritis Staphylococcal infection Urinary tract infection (4 events each) Bacterial infection Cellulitis Diverticulitis Urosepsis (3 events each)

* Spontaneous reports and post-marketing phase IV clinical studies
† The number of patients exposed to abatacept, as estimated from the worldwide sales volume from the international birth date up to the third quarter of 2008 (same hereafter)

In patients treated with infliximab, the incidence of serious infection was 8.4% (32 of 381 subjects) in Japanese clinical studies (e.g., pneumonia [1.6%]), 4.0% (226 of 5706 subjects) in foreign clinical studies (e.g., pneumonia [0.9%], abscess [0.6%], infection tuberculosis [0.3%], and sepsis [0.3%]), and 3.4% (264 of 7678 subjects) in the Japanese post-marketing all-case surveillance (e.g., pneumonia bacterial [1.3%], suspected pneumocystis pneumonia [0.5%], and tuberculosis [0.3%]). In patients treated with etanercept, the incidence of serious adverse events was 6.8% (9 of 132 subjects) in Japanese clinical studies, 11.6% (83 of 714 subjects) in foreign clinical studies, and 0.8% (59 of 7091 subjects) for pneumonia, 0.3% (20 of 7091 subjects) for sepsis, 0.2% (17 of 7091 subjects) for herpes zoster, 0.2% (15 of 7091 subjects) for pneumocystis jiroveci pneumonia, and 0.2% (13 of 7091 subjects) for urinary tract infection in Japanese post-marketing all-case surveillance.

In patients treated with adalimumab, the incidence was 11.8% (45 of 382 subjects) in Japanese clinical studies and 7.1% (86 of 1214 subjects) in foreign clinical studies. In patients treated with tocilizumab, the incidence was 9.0% (39 of 431 subjects) in Japanese clinical studies (e.g., pneumonia [2.3%], herpes zoster [1.9%], cellulitis [0.9%]) and 3.5% (301 of 8509 subjects) in the Japanese post-marketing all-case surveillance.

These results suggested that the incidence of serious infection caused by abatacept tended to be lower than that caused by TNF inhibitors or IL-6 inhibitors. However, taking account of the mechanism of action of abatacept, serious infection is considered to be an important adverse

event requiring particular caution. Therefore, the description of the risk for serious infection will be included, as is the case with other drugs, in the "WARNING," "Important Precaution," and "Clinically significant adverse reactions" sections of the package insert. Also, patients with serious infections will be included in the "CONTRAINDICATIONS," and patients with infections, patients with suspected infections, and immunocompromised patients will be included in "Careful Administration."

PMDA considers as follows:
The cautions against serious infection in the package insert are appropriate. However, further investigation should be performed on the necessity of providing additional cautions upon thorough examination of data on infections collected in the post-marketing surveillance, etc. A non-clinical study raised the possibility that abatacept may affect the defense mechanism against herpes simplex virus, a mechanism that is highly dependent on CD4-positive T cells (Edelmann KH et al, *J Virol*, 75:612-621, 2001). The incidence of herpes infection in foreign pivotal studies was 1.9% in the abatacept group and 1.0% in the placebo group for herpes simples, and 1.5% in the abatacept group and 1.6% in the placebo group for herpes zoster, showing no tendency for an increase in the incidence of serious events in the abatacept group. Therefore, there currently appears to be little necessity for providing cautions focused on this event, but it will be necessary to continuously watch the tendency for occurrence of the event.

ii) Tuberculosis
The incidence of tuberculosis in Japanese and foreign clinical studies and in foreign post-marketing safety reports is shown in Table 32.

Table 32. Tuberculosis in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008)*
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Tuberculosis	0	0	0	1 (<0.1%)	1 (0.1%)	7 (0.2%)	2 events

* Spontaneous reports and post-marketing phase IV clinical study

In patients treated with infliximab, the incidence of tuberculosis was 0.5% (2 of 381 subjects) in Japanese clinical studies, 0.3% (17 of 5706 subjects, including 8 subjects with extrapulmonary tuberculosis) in foreign clinical studies, and 0.3% (22 of 7678 subjects, including 13 subjects with extrapulmonary tuberculosis and 4 subjects with suspected tuberculosis) in the Japanese post-marketing all-case surveillance. In patients treated with etanercept, the incidence was 0% in Japanese clinical studies and 0.1% (10 of 7091 subjects, 8 subjects with pulmonary tuberculosis and 2 subjects with extrapulmonary tuberculosis) in the Japanese post-marketing all-case surveillance. In patients treated with adalimumab, the incidence was 0.5% (2 of 382 subjects) in Japanese clinical studies and 0.7% (9 of 1214 subjects, 3 subjects with disseminated tuberculosis, 1 subject with lymph node tuberculosis, 3 subjects with tuberculosis) in foreign clinical studies. In patients treated with tocilizumab, the incidence was 1.2% (3 of 241 subjects) in Japanese clinical studies and 0.05% (4 of 8209 subjects) in the Japanese post-marketing all-case surveillance.

These results suggested that the incidence of tuberculosis caused by abatacept tended to be lower than the incidences of events caused by TNF inhibitors and IL-6 inhibitors. The package inserts of TNF inhibitors provide cautions against tuberculosis in the "WARNING" and "CONTRAINDICATIONS" sections. However, the package insert of abatacept, as with that of tocilizumab, will not place particular focus on tuberculosis; instead, the cautions will be included in the "WARNING" and "CONTRAINDICATIONS" sections against infection. However, in patients already infected with tuberculosis, the possibility of manifestation or aggravation of symptoms cannot be excluded. Therefore, these patients will be included in the "Careful Administration," and "Important Precautions" will require checks for tuberculosis infection before the administration of abatacept, as is the case with other drugs in the same class.

In foreign clinical studies, tuberculosis occurred despite the strict exclusion criteria against old tuberculosis (patients who had active tuberculosis within the past 3 years and patients who were positive on the tuberculin test and had not received prophylactic chemotherapy were excluded from these studies). Therefore, PMDA asked the applicant to provide detailed data on the 7 patients who had tuberculosis in foreign clinical studies, to explain the effect of abatacept on TNF-α, and to provide further explanation on the appropriateness of the proposed cautions against tuberculosis.

The applicant explained as follows:
Cases of tuberculosis in foreign clinical studies are summarized in Table 33. Of the 7 patients who had the disease, 4 had extrapulmonary tuberculosis, a characteristic observation similar to that in patients treated with TNF inhibitors. There were no cases of disseminated tuberculosis. Tuberculosis was confirmed by bacteriological examination only in 1 patient. Calculation of the annual incidence showed that the incidence have no tendency to increase depending on the duration of exposure to abatacept.

Table 33. List of patients with tuberculosis in foreign cumulative data

Subject No.	Age	Sex	DMARD	Event (PT)	Confirmation of tuberculosis by culture or smear	Date of onset
IM101-102-147-9	39	Female	MTX	Pulmonary tuberculosis	Not confirmed	Day 580 of treatment
IM101-102-164-17	55	Female	MTX	Tuberculosis	Not confirmed	Day 54 of treatment
IM101-031-105-6	47	Female	MTX	Bone tuberculosis	Not confirmed	Day 799 of treatment
IM101-102-94-1	64	Male	MTX	Pulmonary tuberculosis	Confirmed by culture	Day 1331 of treatment
IM101-031-91-16	53	Female	MTX	Lymph node tuberculosis	Not confirmed	Day 1556 of treatment
IM101-031-91-23	63	Female	Sulfasalazine	Pulmonary tuberculosis	Not confirmed	Day 1741 of treatment
IM101-043-13-6	71	Male	MTX	Latent tuberculosis	Not confirmed	Day 523 of treatment

The applicant further explained as follows:
In the immune response to *Mycobacterium tuberculosis*, TNF-α is considered to be produced by the infected macrophages and not the T cells, and the TNF-α produced enhances the phagocytic activity of macrophages themselves, resulting in degradation of *M. tuberculosis* and, at the same time, plays an important role in the formation and maintenance of granulation. Therefore, effects of abatacept on TNF-α production by macrophages were investigated in nonclinical studies. As a results, it has been shown that abatacept does not inhibit TNF-α production by monocytes (macrophages) stimulated with lipopolysaccharides, a cell wall component of *M. tuberculosis* (4.2.1.1-4), and that abatacept does not compete with immune complex-mediated

TNF-α production (4.2.1.1-14). Toxicological studies suggest that, in a mouse model of *M. tuberculosis* infection, abatacept does not significantly affect the defensive capacity of the host against infection by the bacteria. In light of these findings, the risk of abatacept-induced tuberculosis appears to be lower than the risk caused by TNF inhibitors. However, since tuberculosis did occur in patients in foreign clinical studies, involvement of abatacept in the onset of tuberculosis cannot be completely excluded. Thus, the applicant considers that the above cautions should be included in the package insert.

PMDA considers as follows:
The cautions provided against tuberculosis are considered to be appropriate at present. However, because of the higher incidence of the disease in Japan as compared with the US and Europe, it is essential to ensure that patients undergo screening tests for tuberculosis before starting the treatment with abatacept and to pay close attention and monitor for any tendency in the incidence of this disease.

(b) Serious allergic reactions
The incidence of diseases classified as immune system disorders by SOC and the most common events observed in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 34.

Table 34. Immune system disorders in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008) ‡
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Immune system disorders SOC	0	0	5 (2.3%)	43 (2.2%)	13 (1.3%)	192 (4.6%)	Serious allergic reactions (48 events)
Most common events	0	0	Seasonal allergy (5 subjects)	Seasonal allergy (1.0%) Hypersensitivity (0.6%) Drug hypersensitivity (0.2%)	Drug hypersensitivity (0.6%) Seasonal allergy Hypersensitivity (0.3% each)	Seasonal allergy (2.2%) Hypersensitivity (1.5%) Drug hypersensitivity (0.7%) Serious adverse events: Anaphylactic reaction (2 subjects, <0.1%) Anaphylactic shock Polyarteritis nodosa (1 subject each, <0.1%)	Hypersensitivity (23 events) Seasonal allergy Serum sickness Type IV hypersensitivity reaction (1 event each) Serious adverse events: Anaphylactic reaction (23 events) Hypersensitivity (17 events) Anaphylactic shock (4 events) Anaphylactoid reaction Drug hypersensitivity Type I hypersensitivity (1 event each)

‡ Spontaneous reports, post-marketing phase IV clinical study reports, and phase I to III clinical study data

In patients treated with infliximab, the incidence of serious reactions to treatment was 0.5% (2 of 381 subjects) in Japanese clinical studies (1 subject each with anaphylactoid reaction and pulmonary oedema), 0.5% (31 of 2711 subjects) in foreign clinical studies, and 0.4% (30 of 7678 subjects) in the Japanese post-marketing all-case surveillance. Among patients treated with etanercept, no serious allergic reactions were observed in Japanese clinical studies. Among patients treated with adalimumab, no serious allergic reactions were observed in foreign clinical studies, whereas the incidence was 0.3% (1 of 305 subjects) in Japanese clinical studies (dermatitis allergic). Among patients treated with tocilizumab, the incidence of immune system disorders was 3.9% (17 of 431 subjects) in Japanese clinical studies (e.g., anaphylactic shock 0.2% [1 of 431 subjects], anaphylactoid reaction 0.5% [2 of 431 subjects]) and 0.1% (10 of 8509 subjects) in the Japanese post-marketing all-case surveillance (e.g., serious anaphylactic shock, anaphylactic reaction, anaphylactoid reaction).

These results suggested the incidence of serious infections caused by abatacept to be comparable to, or tend to be lower than, the incidence of serious infections caused by TNF inhibitors and IL-6 inhibitors. Cautions against serious allergic reactions will be provided in the "Important Precautions" and "Clinically significant adverse reactions" sections of the package insert.

PMDA considers as follows:
The cautions provided against serious allergic reactions associated with abatacept administration are considered to be appropriate at present. However, adverse immune reactions such as anaphylactic reactions have been observed relatively frequently after market launch in foreign countries, and therefore the necessity of further cautions should be investigated continuously by watching the tendency for the occurrence. It is also important to establish a system in which drug therapy and emergency measures are available for promptly addressing anaphylaxis, etc. prior to treatment with abatacept, and to closely monitor the conditions of the patient [see "4.(ii) Summary of clinical pharmacology studies" for relationship between anti-abatacept antibody and allergic reactions].

(c) Cardiac failure
The incidences of cardiac failure in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 35.

Table 35. Cardiac failure in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008)*
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Cardiac failure	0	0	0	Cardiac failure congestive (5 subjects, 0.3%) Cardiac failure (2 subjects, 0.1%) Serious adverse events: Cardiac failure congestive (4 subjects, 0.2%) Cardiac failure (1 subject, <0.1%)	Cardiac failure congestive (6 subjects, 0.6%) Cardiac failure (1 subject, 0.1%) Serious adverse events: Cardiac failure congestive (5 subjects, 0.5%) Cardiac failure (1 subject, 0.1%)	Cardiac failure congestive (26 subjects, 0.6%) Cardiac failure (9 subjects, 0.2%) Serious adverse events: Cardiac failure congestive (17 subjects, 0.4%) Cardiac failure (5 subjects, 0.1%)	Serious adverse events: Cardiac failure congestive (4 events) Cardiac failure (3 events)

* Spontaneous reports and post-marketing phase IV clinical studies

These results showed that there were no cardiac failure cases in Japanese clinical studies and that, in the foreign pivotal clinical studies, the incidence of cardiac failure was lower in the abatacept group than in the placebo group, which suggested that abatacept was not involved in the occurrence of cardiac failure. In clinical studies of TNF inhibitors in patients with moderate to severe cardiac failure, it was reported that aggravation of cardiac failure and death occurred more frequently in patients treated with TNF inhibitors than in those in the placebo group. Therefore, patients with cardiac failure congestive are included in the ”CONTRAINDICATIONS” section of the package insert of TNF inhibitors. However, the applicant considered that it is unnecessary to provide cautions against cardiac failure congestive in the package insert of abatacept.

PMDA asked the applicant to discuss the risk of abatacept-induced cardiac disorders and provide further justification for the above-proposed package insert, in light of the relatively frequent treatment discontinuation and deaths due to cardiac disorders in the abatacept groups in foreign clinical studies.

The applicant explained as follows:
In foreign pivotal clinical studies, deaths caused by cardiac disorders, including cardiovascular events which were newly identified by re-examination, were observed in 7 of 1995 subjects in the abatacept group (chest pain/death, cardiac failure congestive, hypertensive heart disease, coronary artery atherosclerosis/myocardial ischaemia, death, sudden death, burns third degree/cardiac arrest) and in 3 of 989 subjects in the placebo group (cardiac failure congestive, myocardial infarction, cerebrovascular accident/cardiac arrest). The incidence of treatment discontinuation due to cardiac disorders was also high in the abatacept group, at 0.7% (13 of 1955 subjects), as compared with the incidence in the placebo group, 0.3% (3 of 989 subjects). However, the incidence of cardiac disorders was 5.9% (115 of 1955 subjects) in the abatacept group and 6.3% (62 of 989 subjects) in the placebo group, showing no significant difference between the 2 groups, and the incidence of serious cardiac disorders was 0.9% (18 of 1955 subjects) in the abatacept group and 1.8% (18 of 989 subjects) in the placebo group, being lower in the abatacept group than in the placebo group. Neither was there a tendency for a higher incidence of any specific events in the abatacept group.

In Study IM101-031 in which the safety of abatacept was evaluated in RA patients including those with complications (cardiac failure congestive, chronic obstructive pulmonary disease, diabetes mellitus, asthma) (959 subjects in the abatacept group, 482 subjects in the placebo group), the following data were obtained. Among 18 patients with the complication of cardiac failure congestive (9 subjects in the abatacept group, 9 subjects in the placebo group), cardiac disorders occurred in 22.2% (2 of 9 subjects) in the abatacept group and in 66.7% (6 of 9 subjects) in the placebo group. Similarly, the incidence of cardiac disorders among those with the complication of diabetes mellitus was 6.2% (4 of 65 subjects) in the abatacept group and 16.1% (5 of 31subjects) in the placebo group. Thus, the results did not suggest any tendency for abatacept to cause a higher incidence of cardiac disorders. Furthermore, toxicological studies showed no effect of abatacept on the cardiovascular system, including abnormal laboratory changes such as lipids and blood glucose level. Therefore, abatacept is unlikely to increase the risk of cardiac disorders.

PMDA accepts the applicant’s response as a whole and considers it unnecessary to provide cautions against cardiac disorders including cardiac failure congestive. However, neither the Japanese nor the foreign clinical studies were conducted for a sufficiently long period to allow evaluation of the effects of abatacept on cardiac disorders. In particular, there are only a few experiences of treating patients with severe heart disorders with abatacept, falling short of providing sufficient supportive evidence for the safety of abatacept in treating these patients. Therefore, it is necessary to continue careful investigation on the effects of abatacept on cardiac

disorders in the post-marketing surveillance, etc.

(d) Malignant tumors

The incidences of malignant tumors and the most common events in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 36.

Table 36. Malignant tumors in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008)*
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Neoplasm malignant	0	0	2 (1.0%)	27 (1.4%)	11 (1.1%)	162 (3.9%)	45 events (spontaneous reports, 37 events)
Most common events	0	0	Gastric cancer B cell lymphoma (1 subject each)	Basal cell carcinoma (0.6%) Squamous cell carcinoma of skin (0.2%) Lung cancer (0.2%)	Basal cell carcinoma (0.4%) Breast cancer (0.2%) Endometrial cancer (0.2%)	Basal cell carcinoma (1.4%) Squamous cell carcinoma (0.5%) Squamous cell carcinoma of skin (0.4%) Breast cancer (0.3%)	Lung cancer (5 events), Breast cancer Skin cancer (4 events each) Bladder cancer Malignant melanoma Squamous cell carcinoma (3 events each) Liver carcinoma Lymphoma Thyroid cancer Unspecified malignant neoplasm (2 events each)

* Spontaneous reports and post-marketing phase IV clinical studies

The number of patients with malignant tumors except for skin cancers other than melanoma in the cumulative data of foreign clinical studies was compared with the number predicted from the incidence in the general population in the US (US National Cancer Institute Surveillance Epidemiology and End Results). Results are shown in Table 37. The standardized incidence ratios (SIRs) of lymphoma and lung cancer in the cumulative data of foreign clinical studies were higher than the predicted values in the general population in the US. It is recognized that the incidence of malignant tumors in RA patients is higher than that in the general population. A recent meta-analysis reported that the SIR (95% CI) of the incidences of lymphoma and lung cancer in RA patients relative to those in the general population were 2.08 (1.80, 2.39) and 1.63 (1.43, 1.87), respectively (Smitten A et al. *Arthritis Res Ther*. 2008;10:R45). In light of these observations, there are no study results suggesting an increased risk of malignant tumors caused by abatacept.

Table 37. Number of patients with malignant neoplasms and SIR: Comparison between cumulative data of foreign clinical studies and general population in the US

Neoplasm malignant	Number of patients with malignant neoplasms		SIR (95% CI) [a]
	Cumulative data of foreign clinical studies (observed)	General population in US (predicted) [a]	
Total[b]	82	85.7	0.96 (0.76, 1.19)
Lung cancer	18	11.1	1.62 (0.96, 2.56)
Lymphoma	8	3.5	2.31 (0.99, 4.54)
Breast cancer	12	22.1	0.54 (0.28, 0.95)
Colorectal cancer	3	8.1	0.37 (0.07, 1.09)

a. Predicted number of patients and SIR were corrected for age, sex, and exposure duration.
b. Skin cancers other than melanomas were excluded.

In patients treated with infliximab, the malignant neoplasm incidence was 3.4% (13 of 381 subjects) in Japanese clinical studies (including follow-up period), 1.8% (107 of 5706 subjects) in foreign clinical studies (including follow-up period), and 0.1% (10 of 7678 subjects, 5 subjects with malignant lymphoma, 5 subjects with other malignant tumor) in the Japanese post-marketing all-case surveillance. In patients treated with etanercept, the incidence was 1.4% (2 of 145 subjects, 1 subject each with gastric cancer and hypopharyngeal cancer) in Japanese clinical studies, 0.2% (1 of 454 subjects) for melanoma skin and 0.2% (1 of 454 subjects) for breast cancer in foreign clinical studies, and 0.2% (14 of 7091 subjects) in Japanese post-marketing all-case surveillance. In patients treated with adalimumab, the incidence was 1.3% (5 of 382 subjects, 2 subjects with malignant lymphoma, 3 subjects with malignant tumor other than lymphoma) in Japanese clinical studies and 2.1% (26 of 1214 subjects, 1 subject with lymphoma, 25 subjects with malignant tumor other than lymphoma) in foreign clinical studies. In patients treated with tocilizumab, the incidence was 2.1% (9 of 431 subjects, 2 subjects with large intestine carcinoma, 1 subject each with Hodgkin's disease, breast cancer, breast epithelial cancer, colon cancer, gastric cancer, bladder cancer, and lymphoma) in Japanese clinical studies, and 0.3% (28 of 8509 subjects, including benign neoplasms) in the Japanese post-marketing all-case surveillance.

These results suggest that the incidence of malignant tumors in patients treated with abatacept is comparable to that in those treated with other biological products. Although it is unclear whether or not malignant tumors are caused by abatacept, cautions will be provided in the "WARNING" and "Important Precautions" sections of the package insert, as is the case with other drugs.

PMDA accepts the above response at present. However, as with other biological products, the possibility that the defense mechanism of the host may be affected by abatacept administration cannot be excluded. Therefore, PMDA considers it necessary to continuously investigate the relationship between abatacept and the occurrence of malignant tumors on a large scale and on a long-term basis.

(e) Demyelinating disease

There were no cases with demyelinating disease in Japanese clinical studies, foreign pivotal studies, or foreign post-marketing safety reports on abatacept. Such a disease was observed in only 1 of 4149 subjects (incidence < 0.1%) in the cumulative data of foreign clinical studies.

In subjects treated with infliximab, the incidence was 0% in Japanese clinical studies, 0.04% (2 of 5706 subjects) in foreign clinical studies, 0.003% (3 of 7678 subjects) in the Japanese post-marketing all-case surveillance and, according to foreign post-marketing information (August 24, 1998 to February 23, 2003: estimated number of patients; 240,926 with RA,

179,253 with Crohn's disease, and 12,469 with other inflammatory diseases, 432,647 in total), a total of 143 patients with demyelinating diseases were reported. Among patients treated with adalimumab, there was no demyelinating disease observed in Japanese or foreign clinical studies and, according to the foreign post-marketing information (December 31, 2002 to June 30, 2007; estimated number of patients, 382,942), 65 patients with central demyelinating disease and 11 patients with peripheral demyelinating diseases were reported. Among patients treated with etanercept or tocilizumab, no demyelinating disease was observed in Japanese clinical studies or in Japanese post-marketing all-case surveillances.

Thus, since among patients treated with abatacept, only 1 patient developed demyelinating disease, the applicant considers that it is unnecessary to provide cautions in the package insert.

PMDA accepted the above response.

(f) Lupus-like syndrome and systemic lupus erythematosus

The incidence of lupus-like syndrome and systemic lupus erythematosus in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 38.

Table 38. Lupus-like syndrome and systemic lupus erythematosus in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008) ‡
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Lupus-like syndrome and systemic lupus erythematosus	0	0	0	2 (0.1%)	0	6 (0.1%)	6 events
Most common events				Lupus-like syndrome (1 subject) Systemic lupus erythematosus (1 subject)		Lupus-like syndrome (1 subject) Systemic lupus erythematosus (5 subjects)	Lupus-like syndrome (1 event) Systemic lupus erythematosus (5 events)

‡ Spontaneous reports, post-marketing phase IV clinical studies, and phase I to III clinical studies

In patients treated with infliximab, the incidence of lupus-like syndrome was 0.3% (1 of 384 subjects) in Japanese clinical studies, 0.3% (17 of 5706 subjects) in foreign clinical studies, and 0.04% (3 of 7678 subjects) in the Japanese post-marketing all-case surveillance. In patients treated with etanercept, the incidence of the disease was 0% in Japanese clinical studies, 0.2% (1 of 454 subjects) for discoid lupus erythematosus in foreign clinical studies, and 0.01% (1 of 7091 subjects) in the Japanese post-marketing all-case surveillance. In patients treated with adalimumab, the incidence was 0.3% (1 of 382 subjects) in Japanese clinical studies and 0.3% (4 of 1214 subjects) in foreign clinical studies. Among patients treated with tocilizumab, there were no reports of these diseases in Japanese clinical studies or in the Japanese post-marketing all-case surveillance.

These results show that lupus-like syndrome was not observed in patients treated with abatacept in Japanese clinical studies and suggest that the incidence in foreign pivotal studies tended to be lower than that with TNF inhibitors. In studies on TNF inhibitors, it was reported that the seroconversion of anti-dsDNA antibody was higher in the TNF inhibitor group than in the placebo group and that lupus-like syndrome occurred in association with anti-dsDNA antibody. Therefore, cautions are provided in the "Important Precautions" and "Clinically significant adverse reactions" sections of the package insert. In contrast, the seroconversions of antinuclear antibody (ANA) and anti-dsDNA antibody are lower in the abatacept group than in the placebo group in Japanese and foreign clinical studies (2.7.4.3.2.4). Therefore, the applicant considers that it is unnecessary to provide cautions against lupus-like syndrome in the package insert of abatacept.

PMDA accepts the response of the applicant at present, based on the observation that abatacept caused no increase in the seroconversion of ANA- or anti-dsDNA antibody among other factors. However, since the disease was reported in foreign clinical studies and in post-marketing data, albeit in a limited number of patients, the necessity of further cautions should be investigated continuously by watching the tendency for the occurrence of these disorders.

(g) Psoriasis

The incidence of psoriasis in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 39.

Table 39. Psoriasis in Japanese and foreign clinical studies and foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008) ‡
	Study IM101-071		Long-term extension studies Abatacept N = 217	Double-blind comparative studies		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Psoriasis	0	0	0	10 (0.5%) (includes 1 subject with guttate psoriasis) (severe psoriasis in 1 subject)	0	68 (1.6%) (includes 1 subject with guttate psoriasis)	22 events

‡ Spontaneous reports, post-marketing phase IV clinical studies, and phase I to III clinical studies

The incidence of psoriasis in patients treated with infliximab was 0.1% (1 of 771 subjects) in foreign clinical studies, the incidence of psoriasis in patients treated with etanercept was 0.7% (1 of 145 subjects) in Japanese clinical studies and 0.7% (3 of 454 subjects) in foreign clinical studies, and the incidence with adalimumab was 1 of 2001 patients (dermatitis psoriasiform) in the Japanese early post-marketing phase vigilance. The incidence of psoriasis in patients with tocilizumab was 0% in Japanese clinical studies and 0.04% (3 of 8509 subjects) in the Japanese post-marketing all-case surveillance.

These results suggest that the incidence of psoriasis in patients treated with abatacept tends to be low, as is the case with the incidences in patients with other related drugs, obviating the need for providing cautions in the package insert.

PMDA, in light of a relatively frequent occurrence of psoriasis in foreign clinical studies on abatacept, asked the applicant to investigate whether or not those who developed psoriasis had risk factors such as complications or a past history of psoriasis and to discuss the relationship between the onset of psoriasis and abatacept.

The applicant explained as follows:
Out of 68 subjects who developed psoriasis, identified in the cumulative data of foreign clinical studies, 9 subjects had a past history of psoriasis and their clinical courses were complicated by this disease during the study, and 13 subjects had been treated with TNF inhibitors in the past. Investigation of the use of an antimalarial agent, which is considered to be related to aggravation of psoriasis, or an additional use of NSAIDs showed that 6 subjects had used an antimalarial agent and more than half of the subjects had used NSAIDs before the onset of psoriasis. However, the relationship between the use of these drugs and the onset/aggravation of psoriasis could not be elucidated, due to failure to identify the common risk factor. The relationship between abatacept and the onset of psoriasis is currently unclear. However, given the reports on TNF inhibitor-induced onset of psoriasis (e.g., M J Harrison, W G et al. *Ann Rheum Dis*. 2009;68:209-215.), there is a possibility that abatacept may be involved in the onset of psoriasis by an unidentified mechanism similar to that of TNF inhibitors.

PMDA considers as follows:
In foreign clinical studies, psoriasis was observed only in the abatacept group, and the disease occurred even in patients who did not have a past history or complications of psoriasis. Based on these findings, a causal relationship between the disease and abatacept cannot be ruled out. As regards TNF inhibitors, reports of psoriasis have been accumulated on infliximab, etanercept, and adalimumab, and, accordingly, psoriasis has been added to the "Important Precautions" section of the package insert. The same cautions should be provided for abatacept.

(h) Interstitial pneumonia
The incidence of interstitial pneumonia in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 40.

Table 40. Interstitial pneumonia in Japanese and foreign clinical studies and in foreign post-marketing safety reports on Abatacept

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008)*
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Interstitial pneumonia	1 (0.8%) Non-serious	0	2 (0.9%) (serious interstitial pneumonia in 1 subject)	2 (0.1%) Non-serious	0	12 (0.3%) (serious interstitial pneumonia in 2 subjects)	5 events of serious interstitial lung disease

* Spontaneous reports and post-marketing phase IV studies

The incidence of serious interstitial pneumonia in patients treated with infliximab was 0.3% (1 of 381 subjects) in Japanese clinical studies, 0.02% (1 of 5706 subjects) in foreign clinical studies, and 0.4% (28 of 7678 subjects) in the Japanese post-marketing all-case surveillance; the incidence with etanercept was 2.1% (3 of 145 subjects) in Japanese clinical studies and 0.6% (44 of 7091 subjects) in the Japanese post-marketing all-case surveillance; and the incidence with adalimumab was 1.0% (4 of 382 subjects) in Japanese clinical studies and 0.2% (2 of 1214 subjects) in foreign clinical studies. The incidence in patients treated with tocilizumab was 0.2% (1 of 431 subjects) in Japanese clinical studies and 0.4% (33 of 8509 subjects) in the Japanese post-marketing all-case surveillance.

Interstitial pneumonia is included in the "Careful Administration" and "Clinically significant adverse reactions" sections of the package inserts for other biological products. However, the incidence of this disease in patients treated with abatacept was low in foreign clinical studies and there were few serious cases in either Japan or foreign countries, as shown above. Therefore, the applicant considers that it is unnecessary to provide cautions against interstitial pneumonia in the package insert.

PMDA considers as follows:
The incidence of interstitial pneumonia following abatacept administration is not substantially different from that of other drugs of the same class, and it is appropriate to provide cautions against this disease for abatacept as well. By taking into account the fact that interstitial pneumonia has been reported in patients treated with leflunomide, as an adverse drug reaction unique to Japanese, it is necessary to continue careful investigation on the possible relationship between abatacept and interstitial pneumonia in the post-marketing surveillance, etc.

(i) Blood cell disorders

Neither pancytopenia nor any other serious cytopenia was observed in Japanese clinical studies or foreign pivotal studies on abatacept. In foreign long-term extension studies, pancytopenia was observed in 0.2% (4 of 2340 subjects) and 2 cases were serious (<0.1%). In foreign post-marketing safety reports, 1 case of pancytopenia was noted.

In patients treated with infliximab, the incidence of pancytopenia was 0.3% (1 of 381 subjects) in Japanese clinical studies and 0.04% (2 of 5706 subjects) in foreign clinical studies. Patients treated with etanercept did not develop pancytopenia in Japanese or foreign clinical studies. In patients treated with adalimumab, pancytopenia was not reported in Japanese or foreign clinical studies, but 20 subjects with this disease were reported in the foreign post-marketing information (estimated number of patients, 382,942). Among patients treated with tocilizumab, no cytopenia was observed in Japanese clinical studies. In the Japanese post-marketing all-case surveillance, in contrast, mainly the following cytopenic events were observed: leukopenia (0.3% [25 of 8509 subjects]), neutropenia (0.2% [18 of 8509 subjects]), thrombocytopenia (0.1% [12 of 8509 subjects]), and pancytopenia (0.04% [3 of 8509 subjects]).

Thus, among patients treated with abatacept, no serious cytopenia occurred in Japanese clinical studies, and pancytopenia was observed in only 2 patients (<0.1%) in foreign clinical studies, showing a tendency for a lower incidence than with TNF inhibitors and IL-6 inhibitors. The package insert of adalimumab states that "patients with past or present serious blood dyscrasia (e.g., pancytopenia, aplastic anaemia)" in the "Careful Administration" and the "Clinically significant adverse reactions" sections. Also, the package insert of infliximab includes "white blood cell decreased and neutropenia (frequency unknown)" in the "Clinically significant adverse reactions" section. However, for the reasons presented above, the applicant considers that it is unnecessary to provide such cautions in the package insert of abatacept.

PMDA accepted the applicant's response.

(j) Liver disorder

The incidence of the most common events related to hepatobiliary disorders in Japanese and foreign clinical studies and in foreign post-marketing safety reports on abatacept are shown in Table 41.

Table 41. The most common events related to hepatobiliary disorders in Japanese and foreign clinical studies and in foreign post-marketing safety reports

	Japanese studies			Foreign studies			Foreign post-marketing reports (December 23, 2005 to December 22, 2008)*
	Study IM101-071		Long-term extension study Abatacept N = 217	Double-blind comparative study		Cumulative data Abatacept N = 4149	Estimated number of exposed patients 32,187 person-years
	Abatacept N = 128	Placebo N = 66		Abatacept N = 1955	Placebo N = 989		
Hepatobiliary disorders (SOC)	2 (1.6%)	0	14 (6.5%)	25 (1.3%)	15 (1.5%)	177 (4.3%)	125 events
Most common events	Bile duct stone Cholelithiasis (1 subject each)	-	Cholelithiasis (5 subjects) Hepatic steatosis Gallbladder polyp (3 subjects each)	Cholelithiasis (17 subjects) Biliary colic Hepatomegaly Enlarged liver Hepatic cyst (2 subjects each) Serious adverse events (7 subjects) (0.4%)	Cholelithiasis (7 subjects) Biliary colic (2 subjects) Serious adverse events 3 subjects (0.3%)	Cholelithiasis (1.7%) Hepatic steatosis (0.7%) Cholecystitis (0.4%) Biliary colic (0.3%) Serious adverse events 64 subjects (1.5%)	Liver carcinoma Hepatic failure (2 events each) Hepatitis fulminant Cytolytic hepatitis Hepatitis Liver disorder (1 event each) All were serious

* Spontaneous reports and post-marketing phase IV clinical studies

In patients treated with infliximab, the incidence of hepatobiliary disorders was 1.6% (2 of 129 subjects) in Japanese clinical studies and 6.5% (36 of 555 subjects) in foreign clinical studies. The incidence with etanercept was 0.2% (1 of 454 subjects) for both biliary pain and liver disorder in foreign clinical studies, and 2.4% (167 of 7091 subjects) for hepatic function disorder in the Japanese post-marketing all-case surveillance, and the incidence with adalimumab was 0.4% (9 of 2001 subjects) in the Japanese early post-marketing phase vigilance. The incidence with tocilizumab was 4.6% (20 of 431 subjects) in Japanese clinical studies (e.g., hepatic steatosis 2.1% [9 of 431 subjects], hepatic function disorder 0.9% [4 of 431 subjects]) and 3.9% (328 of 8509 subjects) in the Japanese post-marketing all-case surveillance (e.g., hepatic function abnormal 3.2% [270 of 8509 subjects], liver disorder 0.6% [47 of 8509 subjects]).

The package insert of infliximab includes liver disorder in the “Clinically significant adverse reactions” section, and the package insert of tocilizumab provides cautions related to liver disorders in the “Important Precautions” and “Other Precautions” sections. In contrast, the incidence of adverse events such as hepatobiliary disorders was comparable between the abatacept group and the placebo group in foreign pivotal studies and there have been no serious abnormal laboratory changes suggestive of hepatotoxicity. Therefore, the applicant considers that it is unnecessary to provide cautions against hepatobiliary disorders in the package insert of abatacept.PMDA accepted the above response.

PMDA considers as follows:

Based on the submitted data and the applicant's responses provided above, there is currently little necessity to provide, in the package insert, cautions against demyelinating disease, lupus-like syndrome, blood cell disorder, and liver disorder among the diseases discussed above. However, in view of the fact that, as with other biological products, abatacept affects immune function and suppresses TNF-α and IL-6, the possibility remains that abatacept causes adverse drug reactions similar to those observed with other drugs of the same class. Therefore, it is necessary to carefully evaluate, in the post-marketing surveillance as well, the occurrence of important adverse drug reactions that are known to occur following the administration of other biological products. Also, since the use experience of abatacept is limited at present, compared with other biological products, it is necessary to accumulate sufficient information, particularly on long-term administration, and to further define the safety profile of abatacept. Moreover, it is desirable that a guideline for the use of abatacept be prepared under the collaboration of related academic societies to facilitate the proper use of this drug.

4.(iii).B.(4).2) Safety in the elderly

PMDA asked the applicant to explain the safety of abatacept in the elderly.

The applicant explained as follows:

(a) Age-stratified subgroup analyses in foreign pivotal clinical studies and in the Japanese phase II study (IM101-071) provided the following results: In the foreign pivotal studies, the incidence of adverse events was 89.5% in patients aged ≥65 years and 88.7% in patients aged <65 years in the abatacept group, and 89.2% in patients aged ≥65 years and 84.4% in patients aged <65 years in the placebo group; and the incidence of serious adverse events was 25.1% in patients aged ≥65 years and 11.8% in patients aged <65 years in the abatacept group, and 16.9% in patients aged ≥65 years and 11.8% in patients aged <65 years in the placebo group. In the Japanese study IM101-071, the incidence of adverse events was 55.6% in patients aged ≥65 years and 75.0% in patients aged <65 years in the abatacept 10 mg/kg group, and 84.6% in patients aged ≥65 years and 56.6% in patients aged <65 years in the placebo group; and the incidence of serious adverse events was 22.2% in patients aged ≥65 years and 5.8% in patients aged <65 years in the abatacept 10 mg/kg group, and 30.8% in patients aged ≥65 years and 3.8% in patients aged <65 years in the placebo group. Thus, the incidence of serious adverse events was higher in elderly patients in both the abatacept and the placebo groups, in Japanese as well as in foreign studies.

(b) Detailed analysis of the data of Japanese clinical studies was difficult because of the limited number of elderly patients. In the foreign pivotal studies, investigation of serious adverse events (classified by SOC) observed in elderly patients aged ≥65 years showed that the incidences of "infections and infestations" (5.6% in the abatacept group, 2.7% in the placebo group) and "neoplasms benign, malignant and unspecified" (6.2% in the abatacept group; 2.7% in the placebo group) were higher in the abatacept group than in the placebo group. The finding suggests that the risk of these events tends to increase in the elderly, as a result of decreased physiological functions. Therefore, the elderly will be included in the "Careful Administration" section in the package insert of abatacept, to raise caution against administration in the elderly.

PMDA asked the applicant to explain whether or not there are any new tendencies in the safety profile in the elderly, based on the most current foreign post-marketing safety information.

The applicant explained as follows:

Adverse events that were accumulated, from December 23, 2005 to December 22, 2008 and that were confirmed by medical experts, were compared for reporting frequency of adverse events between the elderly (65-74 years, ≥75 years) and the non-elderly. Results showed the following frequencies of reports (per 100 person years): death, 0.07 in patients aged <65 years, 0.05 in

patients aged 65 to 74 years, and 0.01 in patients aged ≥75 years (same order applies hereafter); serious adverse events, 2.49, 1.03, 0.42; serious infections, 0.57, 0.17, 0.07; and serious neoplasms, 0.12, 0.06, 0.05; showing no tendency for an increase in frequency of reports in the elderly at the current time. Thus, no new findings affecting the safety profile have been obtained in the post-marketing surveillance data accumulated so far. Safety in the elderly will be further investigated by analyzing data collected in the Japanese post-marketing surveillance and the cumulative data of foreign clinical studies that will reflect the results of currently ongoing foreign clinical studies, and by conducting epidemiological studies using foreign databases registering biological products. [18]

PMDA considers as follows:
Abatacept, once marketed, is expected to be administered to elderly patients with various complications, raising the possibility that such complications may be risk factors for infection, etc, in addition to decreased physiological functions. Therefore, in administering abatacept to elderly patients, it is essential to give due consideration to the risk-benefit balance and to closely monitor the clinical course of patients who received the drug. Additional data to be obtained in the future, including those of surveillances in foreign countries, should be provided to medical practice in an appropriate manner.

4.(iii).B.(4).3) Safety in patients with a past history of treatment with other biological products

Since patients previously treated with biological products may have lower tolerability to abatacept as compared with treatment-naïve patients, PMDA asked the applicant to explain the safety in these patients.

The applicant explained as follows:
(a) No study has been conducted to directly compare safety between patients with and without a past history of treatment with biological products. Instead, safety profiles were compared between the foreign study IM101-029 performed in patients who had not adequately responded to TNF inhibitors and the foreign study IM101-102 performed in patients who had not adequately responded to MTX. With the reservation that the treatment durations differed between Study IM101-029 (6 months) and Study IM101-102 (1 year), the following findings were observed: In Study IM101-029, the incidence of adverse events was 79.5% in the abatacept group and 71.4% in the placebo group, and the incidence of serious adverse events was 10.5% in the abatacept group and 11.3% in the placebo group. In Study IM101-102, the incidence of adverse events was 87.3% in the abatacept group and 84.0% in the placebo group, and the incidence of serious adverse events was 15.0% in the abatacept group and 11.9% in the placebo group. Thus, both studies showed a similar relationship in these incidences between the abatacept group and the placebo group, and adverse events that occurred with a high incidence in Study IM101-029 were observed at a high percentage in Study IM101-102 as well.

(b) In the foreign phase III open-label study (IM101-064)[19] which was conducted without a

[18] US, National Databank of Rheumatic Diseases, Anti-Rheumatic Therapy in Sweden registry; Canada, British Columbia RA cohort (IM101-213); Europe, Anti-Rheumatic Therapy in Sweden registry (ARTIS; IM101-125), Rheumatoid Arthritis Observation of Biologic Therapy registry in Germany (RABBIT; IM101-127), Dutch Rheumatoid Arthritis Monitoring (DREAM; IM101-212)

[19] A study conducted to evaluate the efficacy and safety of abatacept in RA patients who had not sufficiently responded to ≥3 months of treatment with TNF inhibitors at the approved dose or in whom administration of TNF inhibitors was discontinued for reasons of safety or tolerability. Abatacept was administered to 449 patients with a past history of treatment with TNF inhibitors and 597 patients currently treated with TNF inhibitors, 1046 patients in total. The above is based on the results obtained within 6 months of treatment.

washout period for TNF inhibitors to collect safety data from a wide range of patients who switched from TNF inhibitors, no significant difference was observed in the adverse event profile between patients with a past history of treatment with TNF inhibitors (those who was not administered TNF inhibitors within 2 months before registration) and those receiving treatment with TNF inhibitors at the time of enrollment. These results suggest that presence or absence of, or a difference in, the past history of TNF inhibitor administration is unlikely to affect the safety of abatacept. Taking account of the finding that the incidence of serious infections tended to increase in patients treated with abatacept and TNF inhibitors [see "4.(iii).A Summary of the submitted data"], the package insert will include cautions against co-administration of abatacept and TNF inhibitors and require close monitoring of patients for signs of infection when TNF inhibitors is switched to abatacept.

PMDA considers as follows:
Because of the difference in the mechanism of action of abatacept from that of other biological products, it is expected that abatacept will be used in many patients by switching from biological products. Therefore, safety in switching products should be evaluated extensively and continuously. Given the similar safety profiles of these products, particular attention should be paid to the safety of patients who switched from other biological products to abatacept especially for the reason of poor tolerability. No information has been obtained on the safety of switching from IL-6 inhibitors in clinical studies of abatacept, but since IL-6 inhibitors and TNF inhibitors exhibit similar effects on immune functions, it will be appropriate to provide cautions on IL-6 inhibitors regarding concomitant use and switching products, as is the case with TNF inhibitors.

4.(iii).B.(5) Post-marketing safety measures
PMDA considers as follows:
Given that the possibility that abatacept may cause adverse drug reactions such as serious infections and malignant tumors cannot be ruled out and that long-term safety remains largely unclear, it will be appropriate to conduct large-scale use-results surveys by registering all patients and their attending physicians and long-term specified use-results surveys of at least 3 years to follow patients for the occurrence of malignant tumors, etc., as for existing biological products. In using abatacept, it is critical to carefully evaluate the risks and benefits and to comply with proper use. For this purpose, it is appropriate to limit the use of abatacept to physicians who have sufficient knowledge of the drug and are experienced in RA treatment. In order to promote the proper use of abatacept, relevant information should be provided to healthcare professionals and patients promptly and appropriately, by providing detailed data to healthcare professionals such as physicians, by preparing patient leaflets containing concise and appropriate explanations of risks and benefits, and by releasing information that becomes available after market launch in a timely manner on the website, etc,

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.2-1.1, 5.3.5.2-1.2). As a result, protocol deviations (failure to perform part of evaluation of target joints), failure to store source documents (some chest X-ray films and breast ultrasonography images), and inconsistency between source documents and case report forms (CRF) (e.g., tender joint counts) were found at some clinical trial sites. Such findings suggested that the sponsor's monitoring had not been appropriately performed in accordance with the standard operating procedures regarding the inconsistency between the above source documents and the CRF. However, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

PMDA considers as follows:

Judging from the submitted data, abatacept is effective for RA patients who have not adequately responded to existing therapies; and the safety of the drug is acceptable given the benefits available. Abatacept, being a biological product with a novel mechanism of action, provides a new treatment option and is therefore of clinical significance. As regards safety, there is a possibility of serious adverse drug reactions such as infection. Therefore, it is necessary to closely monitor the symptoms, etc. of the patient and assess the risks and benefits before administering abatacept. After market launch, long-term specified use-results surveys or other appropriate studies should be conducted to follow the occurrence of infection, malignant tumor, etc., and the obtained information should be provided to physicians and patients in a timely manner.

PMDA considers that abatacept may be approved if it can be concluded, based on comments from Expert Discussion, that there are no particular problems.

Review Report (2)

April 7, 2010

I. Product Submitted for Registration

[Brand Name]	Orencia for I.V. Infusion 250 mg
[Non-proprietary name]	Abatacept (Genetical Recombination)
[Applicant]	Bristol-Myers K.K.
[Date of application]	September 18, 2008

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

PMDA's conclusions described in the Review Report (1) were supported at the Expert Discussion, but PMDA conducted an additional review on the following points and took necessary actions.

(1) Dose

The expert advisors support the following decision of PMDA: although a significant improvement in ACR response, etc., was observed in the abatacept 2 mg/kg group as well in the Japanese study IM101-071, the risk-benefit balance of 2 mg/kg appears to be inferior to that of 10 mg/kg. With serum trough concentrations following 2 mg/kg taken into consideration, only the fixed dose of approximately 10 mg/kg calculated based on body weight should be used for Japanese patients, instead of including 2 mg/kg in the recommended doses.

It was pointed out at the Expert Discussion that since there is a possibility of higher risk of serious infections etc. in the elderly, it is necessary to pay special attention to elderly patients, and therefore cautions should be provided to give consideration to dose reductions in such patients, depending on their conditions. Based on this opinion, PMDA decided it is appropriate to include the description on dose reductions as needed in the elderly in the "Use in the Elderly" section of PRECAUTIONS in the package insert.

(2) Update status of Japanese long-term administration

PMDA asked the applicant to explain the updated status of the Japanese long-term extension study (IM101-129).

The applicant submitted a summary of the interim report on the study up to Week 72 of administration (the date the last subject was observed, [redacted], 20[redacted]), and provided the following explanation:

A total of 217 treated subjects were included in the analysis populations of efficacy and safety. Of the subjects, 26 were withdrawn from the study by Week 72 of treatment. The mean treatment duration throughout the study period was 16.5 months.

ACR 20, 50, and 70 responses, parameters evaluated as efficacy endpoints, were 71.2% (136 of 191 subjects), 46.1% (88 of 191 subjects), and 18.8% (36 of 191 subjects), respectively, at Week 72. The values were maintained at levels similar to those observed at Week 48.

Adverse events (except abnormal laboratory changes) were observed in 93.5% (203 of 217 subjects). No deaths occurred. Serious adverse events were observed in 18.0% (39 of 217 subjects), of which those observed in at least 2 subjects were spinal compression fracture and osteoarthritis (1.4% [3 subjects] each), cellulitis, femur fracture, joint dislocation, joint destruction, cerebral infarction, and interstitial lung disease (0.9% [2 subjects] each).

Adverse drug reactions (except abnormal laboratory changes) were observed in 82.9% (180 of 217 subjects). The most common adverse drug reactions were nasopharyngitis (34.6% [75 subjects]), blood pressure increased (11.5% [25 subjects]), upper respiratory tract inflammation (9.2% [20 subjects]), stomatitis (9.2% [20 subjects]), hypertension (6.0% [13 subjects]), pharyngitis (5.5% [12 subjects]), dental caries (4.6% [10 subjects]), and bronchitis (4.6% [10 subjects]).

Abnormal laboratory changes were observed in 60.4% (131 of 217 subjects). Abnormal laboratory changes, for which a causal relationship to the investigational product can not be ruled out, were observed in 45.2% (98 of 217 subjects). The most common abnormal laboratory changes were white blood cell count increased (16.6% [36 subjects]), lymphocyte count decreased (15.2% [33 subjects]), ALT increased (11.5% [25 subjects]), and white blood cells urine positive (9.2% [20 subjects]), but all were mild or moderate in severity.

Based on the above, the applicant explained that abatacept was well tolerated and efficacy was maintained up to Week 72 of treatment.

PMDA accepted the above response but considers it necessary to continue the evaluation of the safety and efficacy of abatacept with long-term administration via post-marketing surveillance.

(3) Post-marketing surveillance

Since serious infections etc. have been observed following the administration of abatacept, PMDA decided, based on the safety measures taken for existing biological products, that a post-marketing use-results survey in all treated patients should be conducted until data are accumulated from a sufficient number of patients and a long-term specified use-results survey should be conducted to follow the occurrence of infections, malignant tumors, etc., so that medical institutions are well informed of the proper use of the drug and information on adverse drug reactions is thoroughly collected. PMDA asked the applicant to take such measures accordingly.

The applicant explained as follows:
The all-case surveillance will be conducted according to the following methods.

(a) The surveillance will be conducted focusing on serious infections, serious hypersensitivity, autoimmune diseases, and malignant tumors, which are adverse events requiring caution in the administration of abatacept. In addition, taking account of adverse reactions associated with drugs of the same class, additional surveys will be conducted on demyelinating disease, psoriasis, tuberculosis, blood test abnormal, hepatobiliary disorders, cardiac disorders, and interstitial pneumonia. Each patient will be monitored for at least 6 months.

(b) Information will be collected on: (i) the safety and efficacy of abatacept monotherapy, (ii) treatment status, safety, and efficacy in the elderly and low body weight patients, and (iii) safety in switching from other biological products.

(c) Data will be analyzed when information from 3000 patients has been obtained, and the surveillance will be continued until the final evaluation of the regulatory agency is provided. In

addition, a specified use-results survey for a 3-year follow-up period will be conducted by enrolling patients who have completed the all-case surveillance in order to collect long-term information on the occurrence of infection, malignant tumor, etc.

PMDA considered that a post-marketing clinical study should also be conducted to evaluate the suppressive effect of abatacept on structural damage to joints, and therefore asked the applicant to explain a specific study plan.

The applicant explained as follows:
A placebo-controlled, randomized, double-blind study will be conducted in 300 active RA patients who have not adequately responded to MTX. In this study, a fixed dose of abatacept approximately 10 mg/kg calculated based on body weight will be administered under concomitant use of MTX, and the suppressive effect on structural damage to joints will be evaluated at 1 year of treatment using the Genant-modified Sharp score.

PMDA considers that these surveillances and clinical studies should be initiated promptly and results obtained should be provided appropriately to physicians in clinical practice.

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the following indication and the dosage and administration, with the following conditions for approval. The re-examination period is 8 years. The drug substance and the drug product are both classified as powerful drugs, and the product is classified as a biological product.

[Indication] Rheumatoid arthritis (for use only in patients who have not adequately responded to conventional treatments)

[Dosage and administration] The usual adult dosage is the following dose of Abatacept (Genetical Recombination) administered by intravenous infusion. Abatacept is re-administered 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

Patient's body weight	Dose	Number of vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1 g	4

[Conditions for approval]
The applicant is required to:

(1) Conduct a drug use-results survey in all treated patients until data on a certain number of patients have been accumulated in order to collect data on the safety and efficacy of the product in the early post-marketing period, thereby taking necessary measures to ensure proper use of the product.

(2) Conduct a large-scale post-marketing surveillance to thoroughly evaluate the safety of the product and to investigate the safety of long-term treatment with the product and the occurrences of infection, etc.

(3) In order to confirm the efficacy (including the evaluation of prevention of joint destruction progression) and safety of the product, conduct a double-blind comparative post-marketing clinical study using an appropriate control group.