

Report on the Deliberation Results

March 6, 2008

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

[Brand name] Actemra 80 mg for Intravenous Infusion
Actemra 200 mg for Intravenous Infusion
Actemra 400 mg for Intravenous Infusion
[Non-proprietary name] Tocilizumab (Genetical Recombination) (JAN*)
[Applicant] Chugai Pharmaceutical Co., Ltd.
[Date of application] April 28, 2006

[Results of deliberation]

In the meeting held on January 30, 2008, the First Committee on New Drugs concluded that the product may be approved and this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the claimed indications is 5 years 10 months. Actemra 80 mg for Intravenous Infusion and Actemra 400 mg for Intravenous Infusion are classified as biological products and specified biological products, and the drug substance and the drug product are both classified as powerful drugs.

Conditions for approval have been imposed for the indications of the treatment of the following diseases in patients who have had an inadequate response to existing therapies:

Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

1. In post-marketing, conduct a drug use investigation, covering all patients treated with the drug, until data from a fixed number of patients will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.
2. Conduct a large-scale post-marketing survey with a comprehensive investigation of the safety of the drug, including the safety of long-term treatment with the drug and the occurrence of infections etc.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Review Report

January 22, 2008

Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Actemra 80 mg for Intravenous Infusion Actemra 200 mg for Intravenous Infusion Actemra 400 mg for Intravenous Infusion
[Non-proprietary name]	Tocilizumab (Genetical Recombination)
[Name of applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	April 28, 2006
[Dosage form/Strength]	A concentrate for solution for intravenous infusion containing 80 mg, 200 mg, or 400 mg of Tocilizumab (Genetical Recombination) per vial
[Application classification]	Prescription drug (4) Drugs with new indications, (6) Drugs with new doses, (7) Drugs with additional dosage forms, (9) Other drugs
[Items warranting special mention]	Priority review (designated as of July 19, 2006) Expedited review (designated as of July 19, 2006)
[Reviewing office]	Office of New Drug IV

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Review Results

January 22, 2008

[Brand name] (a) Actemra 200 mg for Intravenous Infusion
(b) Actemra 80 mg / 400 mg for Intravenous Infusion

[Non-proprietary name] Tocilizumab (Genetical Recombination)

[Name of applicant] Chugai Pharmaceutical Co., Ltd.

[Date of application] April 28, 2006

[Results of review]

Based on the submitted data, it is judged that the efficacy and safety of the product in the treatment of rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis have been demonstrated.

The efficacy of the product has been shown in Japanese clinical trials etc. Regarding safety, since serious adverse drug reactions such as infections have also been reported, prior to the use of the product, it is necessary to closely observe the patient's symptoms etc. and then carefully determine the risks and benefits and the patient also needs to be fully informed of the risks of the product. Also after the initiation of treatment with the product, it is necessary to monitor the patient's clinical course carefully. After the market launch, it is necessary to conduct a large-scale post-marketing survey covering all patients treated with the product and a long-term, special survey to identify the occurrence of malignancies and infections etc.

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

[Indications]

(a) Actemra 200 mg for Intravenous Infusion

- Treatment of the following diseases in patients who have had an inadequate response to existing therapies:
Rheumatoid arthritis (including the inhibition of progression of structural joint damage),

polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

(The underlined parts are additions to the current text)

(b) Actemra 80 mg / 400 mg for Intravenous Infusion

- Treatment of the following diseases in patients who have had an inadequate response to existing therapies:
Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis
- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

[Dosage and administration]

(a) Actemra 200 mg for Intravenous Infusion

- Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.
- Systemic juvenile idiopathic arthritis, Castleman's disease
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

(The underlined parts are additions to the current text)

(b) Actemra 80 mg / 400 mg for Intravenous Infusion

- Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.
- Systemic juvenile idiopathic arthritis, Castleman's disease
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an

intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

[Conditions for approval]

For treatment of the following diseases in patients who have had an inadequate response to existing therapies:

Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

1. In post-marketing, conduct a drug use investigation, covering all patients treated with the drug, until data from a fixed number of patients will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.

2. Conduct a large-scale post-marketing survey with a comprehensive investigation of the safety of the drug, including the safety of long-term treatment with the drug and the occurrence of infections etc.

Review Report (1)

December 14, 2007

I. Product Submitted for Registration

[Brand name] (a) Actemra 200 for Intravenous Infusion
(b) Actemra 80 / 400 for Intravenous Infusion
(at the time of filing the application)

[Non-proprietary name] Tocilizumab (Genetical Recombination)

[Name of applicant] Chugai Pharmaceutical Co., Ltd.

[Date of application] April 28, 2006

[Dosage form/Strength] A concentrate for solution for intravenous infusion containing 200 mg, 80 mg, or 400 mg of Tocilizumab (Genetical Recombination) per vial

[Proposed indications]

(a) Actemra 200 for Intravenous Infusion

- Reduction in the signs and symptoms, major clinical response, inhibition of progression of structural joint damage, and prevention of disability in rheumatoid arthritis (only in patients who have had an inadequate response to nonsteroidal anti-inflammatory drugs and at least one antirheumatic drug)
- Systemic juvenile idiopathic arthritis
- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

(The underlined parts are additions to the current text)

(b) Actemra 80 / 400 for Intravenous Infusion

- Reduction in the signs and symptoms, major clinical response, inhibition of progression of structural joint damage, and prevention of disability in rheumatoid arthritis (only in patients who have had an inadequate response to nonsteroidal anti-inflammatory drugs and at least one antirheumatic drug)
- Systemic juvenile idiopathic arthritis

- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

[Proposed dosage and administration]

(a) Actemra 200 for Intravenous Infusion

1. Rheumatoid arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

2. Systemic juvenile idiopathic arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks.

3. Castleman's disease

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

(The underlined parts are additions to the current text)

(b) Actemra 80 / 400 for Intravenous Infusion

1. Rheumatoid arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

2. Systemic juvenile idiopathic arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks.

3. Castleman's disease

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

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

For this application, the data submitted by the applicant and the applicant's responses to the questions from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

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

Tocilizumab (Genetical Recombination) (or MRA), the active ingredient of Actemra, is a humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the IgG1 subclass. It was discovered by Osaka University and Chugai Pharmaceutical Co., Ltd. and is produced in Chinese hamster ovary (CHO) cells from a mouse-derived anti-human IL-6 receptor monoclonal antibody using recombinant DNA technology. IL-6 is a cytokine discovered as a humoral factor derived from T cells that induces differentiation of B cells into plasma cells and has been found to have various physiological activities, e.g. inflammatory reactions, induction of differentiation and proliferation of various cells, regulation of immune responses, and thrombocytosis (Akira S, et al. *Adv Immunol.* 1993; 54: 1-78). MRA is expected to exert its therapeutic effects by inhibiting the biological activity of IL-6 and is under development in or outside Japan, as a treatment for rheumatoid arthritis, juvenile idiopathic arthritis, Castleman's disease, Crohn's disease, or multiple myeloma etc. in which IL-6 involvement has been suggested (Yoshizaki K, et al. *Springer Seminars in Immunopathology.* 1998;20:247, etc.). In Japan, Actemra 200 for Intravenous Infusion, an injectable preparation containing MRA as the active ingredient, was approved for the indication of Castleman's disease in April 2005. As of November 2007, MRA is not approved overseas and its marketing authorization applications have just been filed for the treatment of rheumatoid arthritis in the US in November 2007 and in the EU in December 2007.

The clinical development of MRA for the treatment of rheumatoid arthritis (RA) was initiated in ■■■ 19■■■ in Japan and the clinical development for the treatment of systemic juvenile idiopathic arthritis (sJIA) was started in ■■■ 20■■■. As the efficacy and safety of the product in the treatment of RA and sJIA were confirmed in Japanese clinical trials, an application for approval for partial changes to Actemra 200 for Intravenous Infusion and an application for marketing approval for Actemra 80 for Intravenous Infusion and Actemra 400 for Intravenous Infusion, new dosage strengths of Actemra, were filed as of April 28, 2006. For this application, clinical trials involving patients with polyarticular-course juvenile idiopathic arthritis (pJIA) have also been conducted and the applicant positions this disease as pediatric RA and has included pJIA as part of the claimed indication of RA.

In light of the seriousness of sJIA and the unavailability of biologics approved for sJIA in Japan, a notification that the application for sJIA receives a priority review designation was issued from the Ministry of Health, Labour and Welfare (PFSB/ELD Notification dated July 19, 2006). A notification that the application for RA is also to be processed in an expedited manner was issued from the Ministry of Health, Labour and Welfare (PFSB/ELD Notification dated July 19, 2006).

Although the product was submitted for registration as “Actemra 200/80/400 for Intravenous Infusion,” from the point of view of risk management, the brand names were changed from “Actemra 80/400 for Intravenous Infusion” to “Actemra 80 mg/400 mg for Intravenous Infusion” during the regulatory review. As to Actemra 200 for Intravenous Infusion, after a new replacement approval application for changing the brand name to “Actemra 200 mg for Intravenous Infusion” was filed, an application for approval for partial changes was filed as of November 9, 2007.

2. Data relating to quality

The 200 mg preparation of Actemra has already been approved. However, in this application, changes have been made to the manufacturing process, production scale, and manufacturing site for the drug substance and the production scale for the drug product, a manufacturing site for the drug product has been added, the specifications for the drug substance and the drug product have been changed, and new strengths have been added, and the relevant data have been submitted.

2.A Summary of the submitted data

2.A.(1) Drug substance

The manufacturing process for the drug substance, i.e. Actemra solution, has been changed from the manufacturing process for the approved preparation (Actemra 200 for Intravenous Infusion) (Process B [REDACTED]) to a new manufacturing process (Process C). The changes from Process B [REDACTED] to Process C are as follows: (a) Change of the manufacturing facility for [REDACTED] (from Plant A to Plant B), (b) Changes of the cell culture process primarily for improving production yields (the culture scale was changed from [REDACTED] L to [REDACTED] L, [REDACTED], the source of [REDACTED] cholesterol [a medium component] was changed), (c) Changes of the purification process in order to respond to increased production yields (changes to [REDACTED]), and at the same time, the lot of the working cell bank (WCB) was changed, and the risk associated with raw materials of animal origin in the culture media was reduced.

Process C, as with Process B [REDACTED], consists of the cell culture process and the purification process. In the cell culture process, after the thawing of [REDACTED] tubes of the WCB, the cell population is expanded using [REDACTED] in the order of [REDACTED] mL [REDACTED], [REDACTED] mL [REDACTED], [REDACTED] L [REDACTED], and then [REDACTED] L [REDACTED], for seed culture. [REDACTED] L [REDACTED], and the necessary volume of the culture fluid is seeded in [REDACTED] L [REDACTED] and cultured using [REDACTED]. Then, for production culture, the culture fluid in [REDACTED] L [REDACTED] is seeded in [REDACTED] L [REDACTED] and cultured using [REDACTED]. The purification process is the same as that of Process B [REDACTED] except for changes to [REDACTED] etc. [REDACTED], [REDACTED], and [REDACTED] have been defined as critical process steps. Process validation was performed on [REDACTED] commercial scale lots. In the cell culture process, a trend towards cell age-dependent variations in MRA yields or cell viability has not been observed. A characterization study, a genetic stability study, and a purity test of cells at the limit of *in vitro* cell age (CAL) have confirmed the maintenance of the properties of the cells and of the expression construct, and a good consistency of the cell culture process has been demonstrated. In each purification process step, the purity was ascertained by measuring MRA concentration, MRA recovery rate and by [REDACTED].

Of the raw materials used in Process B [REDACTED], the media for the WCB contained components of human or animal origin. In Process C, a subculture medium and a freeze medium for the WCB whose components of animal origin other than galactose have been replaced with those of non-animal origin have been developed and using these media, a new WCB has been established from the approved master cell bank (MCB). Moreover, in Process B [REDACTED], wool-derived cholesterol was used as a medium component in the cell culture process, which has been changed to synthetic cholesterol in Process C.

The drug substance produced by Process C (Lot No. X1) was characterized by peptide mapping for primary structure determination, N-terminal amino acid sequence analysis, C-terminal amino acid sequence analysis, amino acid compositional analysis, determination of the positions of disulfide bonds, molecular weight determination, higher-order structure determination by circular dichroism (CD) spectroscopy, carbohydrate composition analysis, sugar chain mapping, and glycosylation site analysis. The physicochemical properties of the same lot were determined by physical description, ultraviolet (UV) spectrum, the specific absorbance for MRA, SDS-gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), GPC, and ion exchange

chromatography (IEC). Using Lot No. X1 etc., the biological properties of the drug substance produced by Process C were determined including anti-proliferative activity against #ABC cells (#ABC assay), the dissociation constant at human soluble IL-6 receptors, and the binding affinity of MRA to Fc receptors. Product-related substances and product-related impurities in the drug substance produced by Process C (Lot No. X1, etc.) were analyzed by SDS-PAGE, IEF, N-terminal amino acid sequence analysis (Edman degradation), primary structure analysis by peptide mapping, detection of deamidation by [REDACTED], confirmation of sialylated carbohydrate chains, the binding activity to IL-6 receptors, and anti-proliferative activity against #ABC cells in order to elucidate the structure of the peaks observed in IEC and other characteristics. In order to characterize the degradability of the drug substance produced by Process C (Lot No. X2), dimers, multimers, and low molecular weight degradation products formed upon heating and changes in the ion exchange chromatogram of MRA after heating were analyzed and the degradation scheme has been discussed. An investigation of process-related impurities and contaminants has been conducted using [REDACTED] commercial scale lots produced by Process C.

The impact of the drug substance manufacturing process changes on the quality has been discussed based on the results of release testing, comparison of the structures and other characteristics, comparison of the results of in-process tests, and comparison of the results of stability studies. As a result, it has been concluded that there are no differences in all results except for IEC between Process C and Process B [REDACTED]. IEC showed increased #B and decreased #C and #D in Process C compared to Process B [REDACTED], but which has been determined not to affect the quality because the quantitative ratio of isoforms in Process C lies midway between those in Process A and Process B and the drug substances produced by Process A and Process B have been determined to be biologically comparable, the biological properties of Actemra solution are comparable between Process B [REDACTED] and Process C, and the different isoforms have comparable biological activity. Based on these assessment results, the drug substances produced by Process B [REDACTED] and Process C have been determined to be comparable.

In this application, the specifications for the drug substance are proposed for physical description, identification (SDS-PAGE and peptide mapping), pH, purity (related substances, GPC and IEC), bacterial endotoxins test, assay (UV), and potency (#ABC assay). The following changes have been made to the specifications established at the time of the initial approval: (a) Improvement of the test procedure for physical description, (b) Changes to the specification due to the improvement of [REDACTED] in identification test (peptide mapping), (c) Improvement of the analysis method (IEC) for related substances, (d) Changes to the

specification for bacterial endotoxins test, (e) Change of the test procedure for assay from GPC method to UV method, (f) Change of the test procedure to measure the biological activity from assay (the binding activity to IL-6 receptors) to potency assay (#ABC assay).

Along with the manufacturing process changes from Process B to Process C, Actemra solution Lot No. X1 newly produced by Process C has been chosen as an in-house primary reference material of the second generation. The potency of the new in-house primary reference material has been determined to be \times U/mg based on the mean of repeated measurements of the binding activity to IL-6 receptors calibrated against the in-house primary reference material of the first generation.

In order to assess the stability of the drug substance produced by Process C, long-term testing (-50°C, 24 months), accelerated testing (5°C, 6 months), stress testing (temperature [40°C, 3 months]), and stress testing (photostability testing [1.2 million lux · hr + 200 W · h/m²]) were performed with the drug substance produced at a commercial scale (L). The test items in these stability studies were physical description, identification (SDS-PAGE [Coomassie staining and silver staining]), pH, purity (GPC and IEC), polysorbate 80, assay (GPC), assay (UV), assay (the binding activity to IL-6 receptors), and potency (#ABC assay) (Some of the attributes were omitted in the stress testing). The results of these studies were comparable to those on the drug substance produced by Process B. The proposed expiration period for the drug substance is 24 months based on actual data from the long-term testing.

2.A.(2) Drug product

In this application, Actemra 80 mg for Intravenous Infusion and Actemra 400 mg for Intravenous Infusion have been added to the approved preparation, Actemra 200 mg for Intravenous Infusion. These preparations have the same formulation components and concentration (Tocilizumab concentration: 20 mg/mL), but different fill volumes. Actemra 80 mg for Intravenous Infusion is a 10-mL vial filled with 4 mL, Actemra 200 mg for Intravenous Infusion is a 20-mL vial filled with 10 mL, and Actemra 400 mg for Intravenous Infusion is a 20-mL vial filled with 20 mL, and the closure system is a rubber stopper and a flip-off cap.

The drug products are manufactured at manufacturing facility of Plant B and at Plant A. The drug product produced at Plant A using the drug substance solution produced by Process A or Process B at Plant A is referred to as Drug Product 1 (DP1), the drug product produced at Plant A using the drug substance solution produced by Process C at Plant B is referred to as Drug Product 2 (DP2), and the drug product produced at Plant B using the drug substance

solution produced by Process C at Plant B is referred to as Drug Product 3 (DP3). DP2 was used in stability studies on pilot scale lots, Japanese clinical trials (including the extensions), and foreign clinical trials.

The manufacturing processes for the proposed drug products are the same as that for the approved product. Process validation has been performed on [REDACTED] lots of the minimum batch size ([REDACTED] L) and [REDACTED] lots of the maximum batch size ([REDACTED] L) for each preparation produced at [REDACTED] manufacturing facility of Plant B.

The specifications for the drug products are proposed for physical description, identification (SDS-PAGE), pH, purity (related substances [GPC] and [IEC]), foreign insoluble matter test, sterility test, bacterial endotoxins test, insoluble particulate matter test, test for extractable volume, assay (UV), and potency (#ABC assay). In this application, the following changes have been made to the specifications established at the time of the initial approval: The actual volume in container has been changed to the test for extractable volume; an assay (GPC method) has been changed to the assay (UV method); and an assay (the binding activity to IL-6 receptors) has been replaced by potency (#ABC assay). Lot analysis of DP1, DP2, and DP3 has confirmed that DP3 is comparable to DP1.

In order to assess the stability of the drug product, using 3 pilot-scale ([REDACTED]-[REDACTED] L) lots of each fill volume of DP2, long-term testing (5°C, inverted or upright position, 24 months), accelerated testing (25°C, inverted or upright position, 6 months), and stress testing (temperature [40°C, upright position, 3 months, 1 lot of each fill volume], light [upright position, 1.2 million lux · hr + 200W · h/m², 1 lot of the 200 mg preparation], vibration [upright position, 5-50 Hz, up to 60 minutes, 1 lot of the 200 mg preparation]) were conducted. In addition, using DP3 produced at commercial scale ([REDACTED]-[REDACTED] L), long-term testing (5°C, inverted position, 18 months, 3 lots of each fill volume), accelerated testing (25°C, inverted position, 6 months, 1 lot of each fill volume), and stress testing (temperature, light, vibration, [the same number of lots as DP2]) were conducted. The test items tested in these studies are physical description, identification (SDS-PAGE [Coomassie staining and silver staining]), pH, osmotic pressure ratio, purity (GPC, IEC), foreign insoluble matter test, sterility test, bacterial endotoxins test, insoluble particulate matter test, actual volume in container, polysorbate 80 content, assay (GPC, UV, and the binding activity to IL-6 receptors), and potency (#ABC assay) (Some of the attributes were omitted in the stress testings).

The results of long-term testing, accelerated testing, stress testing (light), and stress testing

(vibration) on DP2 and DP3 were comparable to those on the approved preparation (DP1). Although the stress testing (temperature) showed association (increased dimers), an increase in lower molecular weight components (formation of [REDACTED] and [REDACTED]) and increased #A (presumed to be [REDACTED]), and decreased biological activity, there were no differences in the test results among DP1, DP2, and DP3. These study results indicate that the stability of DP2 and DP3 is comparable to that of DP1 and the proposed expiration period is 24 months based on actual data from the long-term testing.

2.B Outline of the review by PMDA

PMDA asked the applicant to explain the reason for replacing the assay of binding activity to IL-6 receptors with the #ABC assay in the specifications for the drug substance and the drug products and to provide a justification for allowing a broader specification range for the #ABC assay compared to the assay of binding activity to IL-6 receptors.

The applicant explained as follows:

While the assay for the binding activity to IL-6 receptors is an ELISA assay that assesses the binding capacity of MRA to IL-6 receptors, the #ABC assay is a cell-based assay that assesses not only the binding capacity of MRA to IL-6 receptors, but also the inhibitory activity on intracellular signal transduction in the IL-6/IL-6 receptor system based on the inhibition of the proliferation of #ABC cells, and is considered a biological activity assay that is better correlated with clinical response. In the stress testing on MRA at 40°C for 3 months, the anti-proliferative activity against #ABC cells was significantly decreased while there was only a slight decrease in the binding activity to IL-6 receptors, which suggested the possibility that the #ABC assay can detect a more subtle change in the activity. Therefore, the binding activity to IL-6 receptors has been replaced by the anti-proliferative activity against #ABC cells in the specifications. Then, (a) Since a biological activity assay using cultured cells has greater variability compared to an immunological binding assay, a broader specification range has been established for the #ABC assay compared to the binding activity to IL-6 receptors, which is considered acceptable for a biological activity assay. (b) As a result of a review based on actual values, the specification range will be changed to “[REDACTED] × [REDACTED] U/mg- [REDACTED] × [REDACTED] U/mg” for Actemra solution ([REDACTED] × [REDACTED] U/mg- [REDACTED] × [REDACTED] U/mg at the time of submission) and “[REDACTED] × [REDACTED] U/mL- [REDACTED] × [REDACTED] U/mL” for the drug product ([REDACTED] × [REDACTED] U/mL- [REDACTED] × [REDACTED] U/mL at the time of submission). (c) There is a plan to improve the precision and robustness of the assay and conduct a study to narrow the specification range in future.

Although the IEC analytical procedure has been improved from the initial application, the

specification limit for [REDACTED] has not been established. PMDA asked the applicant to explain this point.

The applicant explained as follows:

The IEC method at the time of the initial application had problems e.g. variability in [REDACTED] and [REDACTED]. Although the variability in peak area percentage has been improved at the time of filing this application, [REDACTED] is still under investigation and the specification limit for [REDACTED] has not been established. [REDACTED] area percentage will continue to be calculated and recorded and a study to improve the analytical procedure will be continued also after the submission of this application.

PMDA accepted the above response and judged that the specifications, test methods, storage and expiration period for the drug substance and the drug products are appropriate.

3. Non-clinical data

3.(i) Summary of pharmacology studies

The pharmacological effects of MRA, including the mode of action and safety pharmacology studies (general pharmacology studies), have been evaluated also at the time of obtaining the indication of Castleman's disease.

In this application, as the data on the mode of action from primary pharmacodynamic studies, new test results on the dissociation constant of MRA to soluble IL-6 receptors (sIL-6R), the IL-6/sIL-6R complex dissociating effect of MRA, and the effects on other cytokine signal transduction of MRA have been submitted. Also, as the data on the effects in a RA model, the results of an investigation of therapeutic efficacy in a collagen-induced arthritis cynomolgus monkey model have been submitted. No new studies on secondary pharmacodynamics, safety pharmacology, or pharmacodynamic drug interactions have been undertaken.

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

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

3.(i).A.(1).1 Investigation of the mode of action

IL-6 forms a complex with the membrane-bound IL-6 receptor (mIL-6R) or sIL-6R and each complex associates with gp130 on cell membrane and induces intracellular signal transduction.

In the blood and synovial fluid of RA patients, high concentrations of IL-6 and sIL-6R are present and it has been suggested that IL-6 is involved in major symptoms presented by patients (elevated ESR, autoantibody formation, etc.) (Hirano T, et al. *Eur J Immunol.* 1988;18: 1797-1801, Houssiau FA, et al. *Arthritis Rheum.* 1988;31: 784-788, Madhok R, et al. *Ann Rheum Dis.* 1993;52: 232-234, Desgeorges A, et al. *J Rheumatol.* 1997;24: 1510-1516). Similarly to RA patients, sJIA patients also have high serum IL-6 and sIL-6R concentrations and it has been reported that IL-6 contributes to its pathogenesis (De Benedetti F, et al. *J Clin Invest.* 1994;93: 2114-2119, Pignatti P, et al. *J Rheumatol.* 2001;28: 1670-1676, de Benedetti F, et al. *Arthritis Rheum.* 2005;52: 687-693).

MRA has been shown to block intracellular IL-6 signal transduction by inhibiting the binding of IL-6 to its receptor (the data at the time of the initial approval).

a. Binding affinity to sIL-6R (4.2.1.1-1)

It has been confirmed that MRA has binding affinity to mIL-6R (K_d value, about 2-3 nmol/L) (the data at the time of the initial approval). On the other hand, IL-6 and sIL-6R levels are also elevated in the synovial fluid of RA patients, which indicates their involvement in its pathogenesis. Thus, the dissociation constant (K_D value) of MRA (Process C lot) to sIL-6R was determined using a surface plasmon resonance sensor and was 0.713 nmol/L. Similar K_D values were obtained also for Process B ■ lot and Process B ■ lot of MRA.

b. Dissociation of IL-6 from the IL-6/sIL-6R complex (4.2.1.1-2)

When MRA was added to the complexes of recombinant human IL-6 (rhIL-6) and sIL-6R formed *in vitro*, the binding rate of rhIL-6 to sIL-6R was decreased in a MRA concentration-dependent manner and was $\leq 10\%$ at MRA concentrations $\geq 1 \mu\text{g/mL}$. On the other hand, the binding rate of MRA to sIL-6R was increased in a concentration-dependent manner at MRA concentrations from 0.001 to 0.1 $\mu\text{g/mL}$ and reached almost a plateau at $\geq 0.1 \mu\text{g/mL}$. Human IgG₁, a negative control, did not bind to sIL-6R and did not affect the binding rate of rhIL-6 to sIL-6R either.

c. Effects on other cytokine signal transduction (4.2.1.1-3)

The effects of MRA on signal transduction by TNF- α , IL-1 β , and IL-15, which have been shown to be involved in the pathology of RA, and IL-2, which has been shown to be involved in immune system activation, were investigated. The cytotoxic effects of TNF- α on ME-180 cells were observed in a concentration-dependent manner at TNF- α concentrations $\geq 0.3 \text{ ng/mL}$ and the cytotoxic effects of IL-1 β on A375.S2 cells were observed in a concentration-dependent

manner at IL-1 β concentrations ≥ 0.03 ng/mL. The proliferative effect of IL-15 on NK-92 cells was observed in a concentration-dependent manner at IL-15 concentrations ≥ 0.3 ng/mL and the proliferative effect of IL-2 on NK-92 cells was observed in a concentration-dependent manner at IL-2 concentrations ≥ 0.1 ng/mL. Addition of MRA (2-250 $\mu\text{g/mL}$; The mean blood level immediately after intravenous infusion of MRA 8 mg/kg to RA patients was 137 $\mu\text{g/mL}$) had no impact on these effects.

3.(i).A.(1).2) Investigation in a rheumatoid arthritis model

As MRA exhibits neutralizing activity against human and cynomolgus monkey IL-6 receptors, but not against mouse or rat IL-6 receptors (the data at the time of the initial approval), collagen-induced arthritis, which is a commonly used RA model, was induced in cynomolgus monkeys and the therapeutic efficacy of MRA was investigated.

a. A cynomolgus monkey model of collagen-induced arthritis (4.2.1.1-4)

Arthritis was induced in female cynomolgus monkeys by immunization with bovine type II collagen twice and the animals with confirmed arthritis based on swelling of the proximal interphalangeal joints (PIP joints) (the mean oval area of 16 PIP joints of the fore and hind limbs excluding the thumbs) were assigned to the control group (6 monkeys) or the MRA group (8 monkeys). The control group received PBS and the MRA group received 30 mg/kg of MRA intravenously once weekly for 4 weeks. Anti-MRA antibody was detected in 7 out of the 8 animals treated with MRA and 2 of the 7 animals had high antibody levels and plasma MRA levels below the quantification limit after the 4th dose (the animals with high antibody levels).

Joint swelling was assessed based on the mean oval area of the PIP joints. In the control group (6 animals), joint swelling worsened during the treatment period in 3 animals and improved (-14 to -17%) in 3 animals. In the MRA group (8 animals), joint swelling improved in 6 animals (-46 to -93%), worsened transiently after the start of administration and then improved in 1 animal, and kept worsening during the treatment period in 1 animal. This one animal was the animal with high antibody levels.

Joint destruction was assessed using the PIP joints that were assessed for swelling, based on the number of joints with radiographic joint space loss and degeneration (the total score). In the control group, the total score was increased in 3 of the 6 animals and unchanged in the remaining 3 animals. In the MRA group, the total score was increased in 3 of the 8 animals, decreased in 2 animals, and unchanged in 3 animals. The results of radiographic assessment were compared to the results of histopathological assessment of the PIP joints in order to

validate radiographic assessment. As a result, it was shown that the scores of articular cartilage degeneration, fibrosis, formation of granulation tissue, bone destruction, and abnormal bone formation were clearly lower in the joints radiographically assessed as normal than in the joints assessed as abnormal. In the MRA group, the scores of granulation tissue formation and bone destruction tended to be low. The applicant explained that the effects of MRA on radiographic joint destruction were unclear because the inter-animal differences in the radiographic total score were large, some animals had a high score at the first dose, and half of the animals in the control group had no increase in score, which made assessment of progression of joint destruction impossible.

Concerning blood chemistry parameters, there were no clear changes in the parameters other than CRP and albumin, which involve IL-6 in their worsening (ASAT, ALAT, ALP, LDH, total bilirubin, direct bilirubin, total cholesterol, triglyceride). CRP levels were markedly elevated in all animals at the first dose compared to before the first immunization, which were decreased gradually thereafter in the control group, whereas in the MRA group, CRP levels were decreased to the levels before immunization at the 2nd dose in all animals, which were maintained in 6 out of the 8 animals. In the remaining 2 animals, CRP levels were elevated again after the 3rd dose. These 2 animals were those with high antibody levels. Albumin levels were decreased at the first dose compared to before the first immunization in all animals, which did not return to the levels before immunization during the treatment period in the control group, whereas in the MRA group, albumin levels returned to the levels before immunization in 6 out of the 8 animals and the remaining 2 animals without recovery were those with high antibody levels. BAP levels, a bone turnover marker, were elevated in 5 out of the 6 animals in the control group and 7 out of the 8 animals in the MRA group, which were not affected by treatment with MRA.

Plasma IL-6 was not detectable before immunization, but was detected at the first dose in all animals. Plasma IL-6 levels were decreased gradually thereafter in all animals except for 1 animal in the control group while plasma IL-6 levels were markedly elevated after the first dose and then decreased gradually in the MRA group. On the other hand, there were no changes in the plasma sIL-6R level from before immunization throughout the study period in the control group, whereas in the MRA group, there were marked increases in the plasma sIL-6R level after the first dose and a trend towards an increase was maintained in 6 out of the 8 animals. The two animals with decreased plasma sIL-6R levels were those with high antibody levels.

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

PMDA asked the applicant to discuss the mechanism of marked elevations of plasma IL-6 and sIL-6R levels noted after the administration of MRA.

The applicant explained as follows:

Based on the results of an investigation of the binding affinity of MRA to IL-6R, it is inferred that following the administration of MRA to cynomolgus monkeys with collagen-induced arthritis, mIL-6R is occupied by MRA and sIL-6R in blood also forms a complex with MRA. Actually, when plasma radioactivity was analyzed by gel filtration following single intravenous administration of ¹²⁵I-labeled MRA (¹²⁵I-MRA) 5 mg/kg to cynomolgus monkeys, ≥90% of radioactivity was associated with ¹²⁵I-MRA, but most of the remaining radioactivity (4.6-6.9% of radioactivity) was attributable to the ¹²⁵I-MRA/sIL-6R complex (the data at the time of the initial approval). Furthermore, when the elimination rate of ¹²⁵I-hsIL-6R was compared between cynomolgus monkeys pre-treated with MRA and those untreated with MRA, most of plasma ¹²⁵I-hsIL-6R existed as the ¹²⁵I-hsIL-6R/MRA complex from immediately after the administration of ¹²⁵I-hsIL-6R in the animals pretreated with MRA and it was suggested that the elimination rate of the ¹²⁵I-hsIL-6R/MRA complex is slower than that of unbound sIL-6R (untreated with MRA) (in-house data). Thus, it is inferred that elevations of plasma sIL-6R after the administration of MRA are attributable to a slower elimination rate of the sIL-6R/MRA complex compared to unbound sIL-6R (before the administration of MRA). On the other hand, concerning IL-6, IL-6 knockout mice were given infusion of rhIL-6 and while the serum rhIL-6 level was kept constant, a single intraperitoneal dose of anti-mouse IL-6R antibody (MR16-1) was administered (MR16-1 was used because MRA can not bind to mouse IL-6R) and then changes in the serum rhIL-6 level were examined. As a result, the serum rhIL-6 levels were increased up to three-fold after the administration of MR16-1 (in-house data). Therefore, it is inferred that IL-6 continues to be produced at local inflammatory sites etc. also after the administration of MRA, but can not bind to MRA-bound sIL-6R or mIL-6R, which inhibits clearance via IL-6R, resulting in marked elevations of serum unbound IL-6 levels.

The applicant also explained as follows:

Even if plasma sIL-6R levels are elevated following the administration of MRA, as sIL-6R forms a complex with MRA and is unable to bind to IL-6, the therapeutic effects of MRA will be unaffected. Although a high concentration of unbound IL-6 stays in blood, as it seems possible to maintain blood MRA concentrations sufficient to block the biological activity of IL-6 in RA, there should be no possibility that the effects mediated by gp130 occur.

PMDA judged that the pharmacologic effects of MRA against RA and similar diseases, pJIA and sJIA can be explained by the submitted data including the above study results and responses. Although CRP, whose production is induced by IL-6 acting on hepatocytes, is a laboratory parameter that is used as an indicator of the disease activity of rheumatoid arthritis or bacterial infections, it needs to be noted that CRP is decreased following the administration of MRA, regardless of the actual degree of inflammation.

3.(ii) Summary of pharmacokinetic studies

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

In this application, the results of a study assessing the impact of carbohydrate chain on plasma clearance of MRA (4.2.2.7-1) have been submitted.

3.(ii).A.(1) Other pharmacokinetic studies

The amounts of four types of MRA differing in terminal galactose content bound to galactose-binding lectins ([REDACTED], [REDACTED], [REDACTED], [REDACTED]) were determined. As a result, the amount of [REDACTED] (a positive control) bound to each lectin was increased with increasing concentration of the samples added while MRA at concentrations ranging from 1.95 to 500 µg/mL did not bind to any lectin. Therefore, it is inferred that variations in terminal galactose content of MRA do not affect its binding affinity to carbohydrate receptors and carbohydrate receptors contribute insignificantly to the elimination of MRA from plasma.

PMDA judged that there are no particular problems with the above study results.

3.(iii) Summary of toxicology studies

Although the intended patient population includes children in this application, (a) MRA does not crossreact with rats or dogs, which are generally used in juvenile animal toxicity studies, which makes appropriate toxicological evaluation difficult, (b) For juvenile monkey studies, the age of animals (month old), duration of treatment, and experimental conditions etc. have not been established and the 1-month and 6-month repeated dose toxicity studies in cynomolgus monkeys, conducted for the initial approval application, used relatively young animals aged 3-4 years and 2-4 years, respectively, and it was considered that the effects of MRA on young animals that have not reached sexual maturation was also evaluated in these studies. Thus, no new toxicity data have been submitted in this application.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

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

Human pharmacokinetic data were compared retrospectively between the current commercial drug product used in the clinical trials conducted for this application (Process B) and the new to-be-marketed drug product (Process C) and its results have been submitted. These two drug products have been determined to be comparable in terms of the quality test results.

4.(i).A.(1) Comparison of human pharmacokinetics before and after the manufacturing process changes

The investigational product manufactured using the drug substance produced by Process B was used in Japanese phase II studies (5.3.5.1-RA-1, MRA009JP; 5.3.5.1-RA-5, MRA012JP) and a Japanese phase III study (5.3.5.1-RA-4, MRA213JP) in RA patients. The investigational product manufactured using the drug substance produced by Process C was used in a drug interaction study in RA patients (5.3.3.4-1, MRA220JP). Serum Tocilizumab (MRA) concentrations at 4 weeks after the first dose of Tocilizumab 8 mg/kg were compared between these two drug products. As a result, the interindividual variability among the patients treated with the investigational product manufactured using the drug substance produced by Process C (5.65 ± 4.34 $\mu\text{g/mL}$; mean \pm SD) was almost similar to that among the patients treated with the investigational product manufactured using the drug substance produced by Process B (4.88 ± 3.60 $\mu\text{g/mL}$; mean \pm SD).

4.(ii) Summary of results of the human pharmacokinetic and pharmacodynamic studies

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

For this application, as the new evaluation data, the results from Japanese studies in RA patients (5.3.5.2-RA-1, MRA002JP; 5.3.5.4-RA-1, MRA003JP; 5.3.5.1-RA-1, MRA009JP; 5.3.5.4-RA-2, MRA010JP; 5.3.5.1-RA-4, MRA213JP; 5.3.5.1-RA-5, MRA012JP; 5.3.3.4-1, MRA220JP), a Japanese study in pJIA patients (5.3.5.2-RA-2, MRA318JP), and Japanese studies in sJIA patients (5.3.5.2-sJIA-1, MRA011JP; 5.3.5.1-sJIA-1, MRA316JP) have been submitted. As the reference data, the results from foreign studies in RA patients (5.3.5.1-RA-2, LRO300; 5.3.5.1-RA-3, LRO301; 5.3.5.2-RA-3, LRO301A) and a foreign study in sJIA patients (5.3.5.2-sJIA-2, LRO320) have been submitted. The results from *in vitro* studies using human biomaterials (5.3.2.2-1, 5.3.2.3-3) have also been submitted. Unbound MRA concentrations in serum and urine were determined using a validated EIA assay (lower limit of quantification, 1 $\mu\text{g/mL}$ in serum and 15.62 ng/mL in urine). Serum anti-MRA neutralizing antibodies and serum anti-MRA IgE antibodies were determined by EIA using a plate with immobilized [REDACTED] (lower

limit of quantification, [REDACTED] ng/mL in terms of [REDACTED] antibody concentration) and EIA using [REDACTED] bound to [REDACTED] (lower limit of quantification, [REDACTED] UA/mL in terms of standard antigen), respectively, according to validated procedures. Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean±SD.

4.(ii).A.(1) Studies using human biomaterials

IL-6 (20, 500, and 12500 pg/mL) alone or IL-6 (12500 pg/mL) with MRA (250 µg/mL) were added to human hepatocytes and their effects on the levels of expression of liver drug metabolizing enzymes (CYPs) were investigated. As a result, when a high concentration (12500 pg/mL) of IL-6 alone was added, the mRNA expression levels of all CYPs tested (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) except for CYP2E1 were reduced and the reduction was most pronounced for CYP3A4. In the presence of MRA, there were no remarkable changes in the mRNA expression levels of CYPs, which suggested that the reduction of the CYP expression level by a high concentration of IL-6 is suppressed by MRA. When 20 pg/mL of IL-6 alone was added, the mRNA expression level of CYP2C19 was increased, but the mRNA expression levels of other CYPs remained unchanged. When 500 pg/mL of IL-6 alone was added, the mRNA expression level of CYP3A4 was decreased and the mRNA expression levels of CYP2C19, CYP2D6, and CYP2E1 were increased. Although the cause for varying effects on the expression levels of CYPs depending on the IL-6 concentration is unknown, since an *in vivo* study (5.3.3.4-1, MRA220JP) has suggested that the expression levels of CYP2C19 and CYP3A4 are increased following the administration of MRA in RA patients, it has been inferred that the expression levels of at least CYP2C19 and CYP3A4 are lowered at the physiological concentrations of IL-6 in the intended patients for MRA and the reduction of the expression levels of these enzymes is suppressed by the administration of MRA (5.3.3.2-1).

As the manufacturing process was changed from the approved process B-2 to Process C, the binding affinity of MRA to Fc receptors expressed on human peripheral blood mononuclear cells was compared between the drug substances produced by Process B-2 and Process C. As a result, there were no differences between the two processes. The effects of human IgG (10-1000 nmol/mL) on the binding of MRA produced by Process B-2 (¹²⁵I-labeled MRA, 10 nmol/mL) to Fc receptors were investigated. As a result, the amount of MRA bound to Fc receptors in the presence of human IgG (1000 nmol/mL), which corresponds to 100 times the concentration of MRA, was 6.6 % of that in the absence of human IgG. The amount of MRA bound to all mononuclear cells present in 1 mL of human blood (assuming 0.456×10^6 cells) was estimated at 0.0017 ng, which was extremely low compared to 1 µg/mL, i.e. the minimum effective blood

concentration of MRA. Based on the above, it was considered that the binding of MRA to Fc receptors is largely inhibited by endogenous IgG in human serum where there is an excess of endogenous IgG (8-18 mg/mL) in relation to MRA (5.3.2.3-3).

4.(ii).A.(2) Studies in RA patients

Japanese data

4.(ii).A.(2).1) Phase I/II study (5.3.5.2-RA-1, MRA002JP)

The pharmacokinetic parameters in Japanese RA patients (5 patients per group) who received three intravenous doses of 2, 4, or 8 mg/kg of MRA at 2-week intervals are as shown in the following table and MRA had non-linear pharmacokinetics, which was considered attributable to decreased clearance via IL-6 receptors due to the saturation of the receptors with increasing dose of MRA.

Table. Serum MRA parameters following repeated intravenous doses of MRA in Japanese RA patients

		C _{1hr} (µg/mL)	T _{1/2} (hr)	AUC _{finite} (hr·µg/mL)	CL _{total} (mL/hr)
1st dose	2 mg/kg	43.6 ± 10.1	74.4 ± 18.3	3440.4 ± 822.5	28.8 ± 10.9
	4 mg/kg	49.0 ± 12.6	96.9 ± 50.2	4663.4 ± 2184.9	50.6 ± 33.2
	8 mg/kg	82.5 ± 32.4	160.2 ± 34.3	10660.8 ± 4069.7	30.5 ± 11.9
2nd dose	2 mg/kg	44.0 ± 9.1	77.0 ± 13.9	3571.5 ± 800.8	26.7 ± 9.0
	4 mg/kg	55.1 ± 12.3	122.2 ± 64.2	5669.3 ± 2754.2	42.2 ± 29.9
	8 mg/kg	105.6 ± 36.6	191.5 ± 45.6	16995.8 ± 8233.8	18.6 ± 7.7
3rd dose	2 mg/kg	27.9 ± 12.3	86.6 ± 18.4*	3013.5 ± 1069.8	28.2 ± 11.1*
	4 mg/kg	49.5 ± 10.1	139.8 ± 71.1	6035.3 ± 3200.3	40.7 ± 34.7
	8 mg/kg	129.9 ± 48.1	241.8 ± 71.4	19939.0 ± 8900.3	13.5 ± 5.3

n=5, *,n=4

Serum CRP declined rapidly following the administration of MRA and normalized (<1 mg/dL) on Day 7 in all groups, but rose again on Day 14 in the 2 and 4 mg/kg groups. When serum MRA levels were maintained at ≥1 µg/mL (lower limit of quantification), CRP normalized at most of the sampling points, which suggested that ≥1 µg/mL of serum MRA is required for the inhibition of IL-6 signal transduction by MRA.

The serum IL-6 concentrations increased following the administration of MRA and declined with decreasing concentrations of serum MRA. The serum soluble IL-6 receptor (sIL-6R) concentrations were elevated after the administration of the 1st dose of MRA and the elevated levels were maintained up to the last sampling point (Day 42). Whether sIL-6R in serum exists in a bound or unbound form following the administration of MRA was investigated by gel filtration method. As a result, ≥90 % of sIL-6R was bound to MRA at serum MRA concentrations ≥1 µg/mL, suggesting the formation of the immune complexes. It was inferred that elevations of serum sIL-6R after the administration of MRA were attributable to a

prolonged elimination half-life of sIL-6R due to the formation of the immune complexes of sIL-6R with MRA [see “3.(i).B *Outline of the review by PMDA*”].

4.(ii).A.(2).2 Extension study of the phase I/II study (5.3.5.4-RA-1, MRA003JP)

Patients continuing from the phase I/II study (15 subjects) received intravenous MRA at a dose of 8 mg/kg as a rule every 4 weeks (Adjustments in the dose and dosing interval were allowed according to clinical symptoms and changes in clinical laboratory values, the maximum dose per administration was 8 mg/kg, the minimum dosing interval was 2 weeks). As a result, serum CRP normalized at most of the sampling points when serum MRA trough concentrations were ≥ 1 $\mu\text{g/mL}$ and it was confirmed that the minimum effective serum MRA concentration is 1 $\mu\text{g/mL}$ also in the long-term treatment, as in the short-term treatment.

4.(ii).A.(2).3 Late phase II study (5.3.5.1-RA-1, MRA009JP)

When Japanese RA patients (109 subjects) received a total of three intravenous doses of 4 or 8 mg/kg of MRA at 4-week intervals, the serum MRA trough concentration in the 4 mg/kg group was below the lower limit of quantification in all subjects (52 subjects) at 4 weeks after the 1st dose, in 48 of 49 subjects at 4 weeks after the 2nd dose, and in 45 of 47 subjects at 4 weeks after the 3rd dose, and ≥ 1 $\mu\text{g/mL}$ of serum MRA trough concentrations could not be maintained in most subjects. On the other hand, the serum MRA trough concentration in the 8 mg/kg group was ≥ 1 $\mu\text{g/mL}$ in 31 of 53 subjects at 4 weeks after the 1st dose, in 34 of 50 subjects at 4 weeks after the 2nd dose, and in 37 of 48 subjects at 4 weeks after the 3rd dose, and the mean serum MRA concentration in the subjects with detectable MRA was 3.2 ± 4.3 $\mu\text{g/mL}$, 6.8 ± 7.1 $\mu\text{g/mL}$, and 9.3 ± 8.7 $\mu\text{g/mL}$, respectively.

Pharmacokinetic parameters were calculated for each individual, using serum MRA concentrations after the 3rd dose (a model-independent analysis). The $\text{AUC}_{\text{finite}}$ was 9028.72 ± 3982.87 $\text{hr}\cdot\mu\text{g/mL}$ in the 4 mg/kg group and 32073.73 ± 10818.55 $\text{hr}\cdot\mu\text{g/mL}$ in the 8 mg/kg group and the $C_{1\text{h}}$ (the serum MRA concentration at 1 hour post-dose) was 72.33 ± 16.07 and 160.25 ± 36.48 $\mu\text{g/mL}$, respectively, and a more than dose proportional increase in the AUC was observed.

Since the serum CRP concentrations normalized at all sampling points when the serum MRA trough concentrations were maintained at ≥ 1 $\mu\text{g/mL}$, the minimum effective serum MRA concentration for the inhibition of IL-6 signal transduction was considered to be 1 $\mu\text{g/mL}$.

4.(ii).A.(2).4) Extension study of the late phase II study (5.3.5.4-RA-2, MRA010JP)

Patients continuing from the late phase II study (144 subjects) received intravenous MRA at a dose of 8 mg/kg as a rule every 4 weeks (Adjustments in the dose and dosing interval were allowed according to clinical symptoms and changes in clinical laboratory values, the maximum dose per administration was 8 mg/kg, the minimum dosing interval was 2 weeks). As a result, the serum MRA trough concentrations remained <50 µg/mL over time in many subjects. The CRP normalized at most of the sampling points when the serum MRA concentrations were ≥1 µg/mL, whereas the CRP did not normalize at some sampling points even when the serum MRA concentrations were maintained at ≥1 µg/mL.

4.(ii).A.(2).5) Phase III, double-blind, comparative study (5.3.5.1-RA-4, MRA213JP)

When Japanese RA patients (61 subjects included in the pharmacokinetic analysis) received MRA 8 mg/kg every 4 weeks for 24 weeks, the percentage of patients with serum MRA trough concentrations ≥1 µg/mL was 71.7 % (43 of 60 subjects) at 4 weeks after the 1st dose, 79.2 % (38 of 48 subjects) at 4 weeks after the 2nd dose (at 8 weeks after the 1st dose), 82.6 % (38 of 46 subjects) at 4 weeks after the 3rd dose (at 12 weeks after the 1st dose), and 85.0-89.6 % thereafter. The mean serum MRA concentration rose with increasing number of doses after the 1st dose, but remained almost constant after Week 12 as shown in the following table. Also, in individual patients, the maximum serum MRA concentrations were 28.6-33.3 µg/mL and the minimum concentrations were 1.12-1.20 µg/mL after Week 12. Therefore, it was considered that serum MRA trough concentrations were almost constant after Week 12.

Table. Serum MRA trough concentrations following repeated intravenous doses of MRA 8 mg/kg every 4 weeks in Japanese RA patients

Weeks after the 1st dose	4	8	12	16	20	24
No. of quantifiable cases	43	38	38	43	43	34
Serum MRA trough concentration (µg/mL)	5.14 ± 3.98	8.36 ± 4.64	9.64 ± 6.27	10.6 ± 7.01	11.1 ± 6.72	12.7 ± 7.04

Mean ± SD

4.(ii).A.(2).6) Phase III, randomized, comparative study (5.3.5.1-RA-5, MRA012JP)

When Japanese RA patients (157 subjects included in the pharmacokinetic analysis) received MRA 8 mg/kg every 4 weeks for 52 weeks, serum MRA trough concentrations at different sampling points are as shown in the following table and the percentage of subjects with serum MRA concentrations ≥1 µg/mL was 59.6 % (81 of 136 subjects) at 4 weeks after the 1st dose, 90.1 % (109 of 121 subjects) at 4 weeks after the 4th dose (at 16 weeks after the 1st dose), and 87.6-93.9 % thereafter. The mean serum MRA concentration rose with increasing number of

doses after the 1st dose and its time course is presented in the following table. Also, in individual patients, the maximum serum MRA concentrations were 33.1-47.7 µg/mL and the minimum concentrations were 1.00-1.43 µg/mL after Week 20. Therefore, it was considered that serum MRA trough concentrations were almost constant after Week 20.

Table. Serum MRA trough concentrations following repeated intravenous doses of MRA 8 mg/kg every 4 weeks in Japanese RA patients

Weeks after the 1st dose		4	8	12	16	20	24	28	32	36	40	44	48	52
No. of quantifiable cases		81	98	107	109	108	99	100	98	107	93	100	101	87
Serum MRA trough concentration (µg/mL)	Mean	5.10	7.94	9.82	9.92	11.1	12.3	11.9	12.5	12.7	13.1	12.8	13.4	15.1
	SD	3.52	5.85	7.45	6.96	7.14	8.58	7.52	8.14	8.28	8.32	8.02	7.98	8.64

The serum IL-6 level increased transiently at 4 weeks after the 1st dose and then decreased. The serum sIL-6R was elevated after the administration of MRA and the elevated level was maintained up to the last sampling point (at 52 weeks after the 1st dose).

4.(ii).A.(2).7) Open-label clinical study in pJIA patients (5.3.5.2-RA-2, MRA318JP)

When Japanese pJIA patients received three intravenous doses of MRA 8 mg/kg at 4-week intervals, the percentage of subjects with serum MRA concentrations ≥ 1 µg/mL and the mean trough concentration were 11 of 18 subjects (61.1 %) and 3.83 ± 3.47 µg/mL, respectively, at 4 weeks after the 1st dose, 11 of 17 subjects (64.7 %) and 5.71 ± 5.71 µg/mL, respectively, at 4 weeks after the 2nd dose (at 8 weeks after the 1st dose), and 11 of 18 subjects (61.1 %) and 4.88 ± 4.68 µg/mL, respectively, at 8 weeks after the 2nd dose (at 12 weeks after the 1st dose). The serum CRP concentrations normalized at most of the sampling points when the serum MRA trough concentration were ≥ 1 µg/mL, which was similar to the results of the studies in RA patients.

4.(ii).A.(3) Studies in sJIA patients

4.(ii).A.(3).1) Early phase II study (5.3.5.2-sJIA-1, MRA011JP)

Japanese systemic JIA (sJIA) patients (11 subjects) aged between 2 and 20 years (under 16 years of age at onset) received intravenous ascended doses of 2, 4, and 8 mg/kg of MRA at 2-week intervals by inpatient titration method (If a test performed at or after 5 days of the initial dose or the second dose [if the same dose is continued] of each dose level showed that the CRP was not decreased to < 1.5 mg/dL, increase the dose to the next level. Otherwise, the same dose was used. The final dose was given 3 times). As a result, the mean serum MRA concentration before the administration of the 3rd dose at the final dose level was < 1 µg/mL at 2 mg/kg (3 subjects) (below the lower limit of quantification in all the 3 subjects), 10.57 ± 5.98 µg/mL at 4 mg/kg (5

subjects) (below the lower limit of quantification in one subject), and 13.83 ± 6.87 $\mu\text{g/mL}$ at 8 mg/kg (3 subjects). Thus, it seemed that 8 mg/kg/2 wk can maintain ≥ 1 $\mu\text{g/mL}$ of serum MRA concentrations in all subjects. Furthermore, when treatment was continued, allowing adjustments in the dosing interval/the dose, the serum MRA concentrations were ≥ 1 $\mu\text{g/mL}$ at all sampling points after Week 8 in all subjects and the CRP normalized at most of the sampling points.

There was no clear correlation between the serum MRA concentration and the serum IL-6 concentration, and the serum sIL-6R level was elevated after the administration of MRA, but the interindividual variability was greater compared to the results of the studies in RA patients.

4.(ii).A.(3).2 Phase III study (5.3.5.1-sJIA-1, MRA316JP)

Japanese sJIA patients (56 subjects) aged between 2 and 20 years (under 16 years of age at onset) received three intravenous doses of MRA 8 mg/kg at 2-week intervals and those who achieved CRP < 0.5 mg/dL and a 30% improvement in the JIA core set on the last observation day entered the double-blind phase (the transition period was 0 or 1 day) and received six intravenous doses of MRA 8 mg/kg or placebo at 2 week-intervals. As a result, during the open-label phase, 53 of 56 subjects at 2 weeks after the 1st dose and 46 of 50 subjects at 6 weeks after the 1st dose had serum MRA concentrations ≥ 1 $\mu\text{g/mL}$. During the double-blind phase, all of the subjects treated with MRA had serum MRA concentrations ≥ 1 $\mu\text{g/mL}$ until 2 weeks after the last dose, while the number of subjects with serum MRA concentrations ≥ 1 $\mu\text{g/mL}$ in the placebo group was 15 of 20 subjects at 4 weeks after the last dose of MRA (2 weeks prior to the start of the double-blind phase), 8 of 15 subjects at 6 weeks after the last dose of MRA, and 0 of 14 subjects at 7 weeks after the last dose of MRA. The AUC_{last} during the open-label phase (calculated with all subjects) increased with increasing number of doses and was $21\,722.5 \pm 7201.0$ after the 1st dose, 27898.1 ± 12328.3 after the 2nd dose, and 30564.4 ± 11897.5 hr- $\mu\text{g/mL}$ after the 3rd dose. The $t_{1/2}$ after the last dose in the open-label phase (calculated with the subjects randomized to placebo where the elimination phase can be assessed) was 121.7 ± 31.9 hr. The serum MRA concentration reached steady state between Week 8 and Week 14 in 14 of 20 subjects treated with MRA and the mean steady-state concentration was 57.4 ± 20.6 $\mu\text{g/mL}$. Meanwhile, the serum MRA concentration in the 6 subjects who did not reach steady state was 33.9 ± 9.30 $\mu\text{g/mL}$ (n=5) at 14 weeks after the 1st dose and 47.5 ± 11.7 $\mu\text{g/mL}$ (n=5) at 18 weeks after the 1st dose, indicating that the elimination rate may be faster in these subjects compared to those who reached steady state.

4.(ii).A.(4) Intrinsic factor PK study

When Japanese RA patients with renal impairment (mild, 4 subjects; moderate, 5 subjects; severe, 3 subjects) and Japanese RA patients with normal renal function (2 subjects) received a single intravenous dose of MRA 8 mg/kg, the pharmacokinetic parameters of serum MRA in different patient groups are as shown in the following table. When the serum MRA trough concentration at 4 weeks post-dose was compared between the subgroups of RA patients considered to have normal renal function from Studies MRA009JP, MRA213JP, and MRA012JP and this study population, the variations in the trough concentrations obtained in this study were within the inter-individual variability among the RA patients considered to have normal renal function. Thus, it was considered that the pharmacokinetics of MRA is not significantly affected by the renal function.

Table. Serum MRA parameters after the administration of MRA in patients with renal impairment

Renal function (n)	C _{1h} * (µg/mL)	t _{1/2} (hr)	AUC _{last} (hr·µg/mL)	CL (mL/hr/kg)
Mild (4)	174.0 ± 29.1	101.2 ± 38.41	20816.0 ± 9334.4	0.49 ± 0.35
Moderate (5)	177.0 ± 18.9	143.3 ± 51.5	24796.2 ± 7710.3	0.34 ± 0.11
Severe (3)	172.3 ± 35.0	148.0 ± 14.5	28728.7 ± 10061.9	0.29 ± 0.10
Normal (2)	176.0 ± 25.5	118.9 ± 15.2	23417.7 ± 3472.3	0.34 ± 0.06

*: C_{4h} for one subject only (a patient with moderate renal impairment)

4.(ii).A.(5) Extrinsic factor PK study

4.(ii).A.(5).1 Drug interaction study (5.3.3.4-1, MRA220JP)

Japanese RA patients with CRP ≥ 1.5 mg/dL suggestive of clearly excessive IL-6 signal transduction received a single oral dose of dextromethorphan hydrobromide 30 mg (CYP3A4 group, 13 subjects) or omeprazole 10 mg (CYP2C19 EM¹ group [including IM], 13 subjects; CYP2C19 PM group, 5 subjects) on Day 0 and Day 14 and a single intravenous dose of MRA 8 mg/kg on Day 7, and the effects of the inhibition of IL-6 signal transduction by MRA on CYP3A4 and CYP2C19 were investigated.

There was a negative correlation between the serum MRA concentration and the CRP following a single dose administration of MRA, and the CRP declined and normalized after the administration of MRA in each subject. Then, when the serum MRA concentration was decreased to < 1 µg/mL, the CRP level was elevated, and it was confirmed that IL-6 signal transduction is inhibited when the serum MRA concentration is ≥ 1 µg/mL. Since CRP normalized in all subjects on Day 14, it is considered that IL-6 signal transduction was inhibited

¹ EM (Extensive Metabolizer): CYP2C19*1/*1(Wild-type)
IM (Intermediate Metabolizer): CYP2C19*1/*2, *1/*3
PM (Poor Metabolizer): CYP2C19*2/*2, *2/*3, *3/*3

by MRA. An investigation of the effects of the inhibition of IL-6 signal transduction on CYPs by this design was justified.

a. Effects on the pharmacokinetics of omeprazole

The pharmacokinetic parameters of plasma omeprazole on Day 0 and Day 14 are as shown in the following table and the C_{max} , the AUC_{last} , and the $t_{1/2}$ decreased and the CL/F increased in the CYP2C19 EM group, indicating that the expression level of CYP2C19 was increased due to the inhibition of IL-6 signal transduction by MRA. In the CYP2C19 IM group, changes in the C_{max} , the AUC_{last} , and the $t_{1/2}$ were not significant, but there was a trend towards decreases and the CL/F tended to increase. Also in the CYP2C19 PM group, a similar trend as in the CYP2C19 IM group was noted, which was inferred to be attributable to an increase in the CL/F of omeprazole resulting from an increased expression level of CYP3A4 due to the inhibition of IL-6 signal transduction by MRA, as it has been reported that CYP3A4 is also involved in the metabolism of omeprazole.

Table. Pharmacokinetic parameters of plasma omeprazole without or with MRA

		C_{max} (ng/mL)	$t_{1/2}$ (hr)	AUC_{last} (hr•ng /mL)	CL/F (L/hr)
EM	Day 0	417.2 ± 216.6 (8)	1.06 ± 0.76 (7)	844.1 ± 909.3 (8)	15.53 ± 8.97 (7)
	Day 14	211.9 ± 204.6 (8)	0.79 ± 0.54 (4)	443.2 ± 703.9 (8)	26.23 ± 14.94 (4)
IM	Day 0	585.9 ± 271.2 (5)	1.42 ± 0.79 (4)	1461.6 ± 1101.4 (5)	6.77 ± 3.39 (4)
	Day 14	556.7 ± 321.4 (5)	1.16 ± 0.62 (5)	1123.5 ± 860.8 (5)	14.04 ± 11.81 (5)
PM	Day 0	612.1 ± 221.1 (5)	2.43 ± 1.05 (5)	2545.8 ± 2032.7 (5)	4.81 ± 2.06 (5)
	Day 14	563.5 ± 171.5 (5)	1.94 ± 0.52 (5)	1679.1 ± 775.9 (5)	6.18 ± 2.11 (5)

Mean ± SD (n)

b. Effects on the pharmacokinetics of dextromethorphan and its metabolites

The pharmacokinetic parameters of plasma dextromethorphan and its metabolite, dextrorphan on Day 0 and Day 14 are as shown in the following table. Although the administration of MRA had no effects on the pharmacokinetics of plasma dextromethorphan, the plasma dextrorphan concentration was decreased. It has been reported that dextromethorphan is metabolized to 3-methoxymorphinan by CYP3A4 and dextrorphan by CYP2D6 and furthermore, 3-methoxymorphinan and dextrorphan undergo secondary metabolism by CYP2D6 and CYP3A4, respectively. Therefore, the above results suggest the possibility that the inhibition of IL-6 signal transduction by MRA affected the expression of CYP2D6, a metabolizing enzyme of dextromethorphan or the expression of CYP3A4, a metabolizing enzyme of dextrorphan.

Table. Pharmacokinetic parameters of plasma dextromethorphan and dextrorphan without or with MRA

		C _{max} (ng/mL)	t _{1/2} (hr)	AUC _{last} (hr•ng /mL)	CL/F (L/hr)
Dextromethorphan	Day 0	2.76 ± 3.19	6.66 ± 2.07	20.0 ± 27.9	2343 ± 2017
	Day 14	2.17 ± 2.36	7.63 ± 2.10	18.2 ± 23.3	2585 ± 2347
Dextrorphan	Day 0	7.45 ± 4.32	3.09 ± 0.93	27.5 ± 16.6	1037 ± 726
	Day 14	4.36 ± 2.04	3.01 ± 0.76	17.9 ± 9.0	1417 ± 933

n=13 Mean ± SD

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

4.(ii).B.(1) **Pharmacokinetics of MRA and the dosage regimen**

Since the proposed dosage regimen of MRA is different between RA/pJIA (every-4-week administration) and sJIA (every-2-week administration), PMDA asked the applicant to explain the dosing rationale for each disease, and provide its justification by comparing the blood MRA concentrations etc. among the different diseases.

The applicant explained as follows:

For RA, a dosing interval of 2 weeks, which is likely to maintain effective blood levels, was selected for a phase I/II study, as in the case of Castleman's disease (MCD). However, when a simulation was performed based on the relationship between the serum MRA trough concentration and CRP in this study, it was predicted that the inhibition of IL-6 action can be maintained using even an every-4-week administration regimen at a dose of 8 mg/kg. And in a late phase II study, when placebo, MRA 4 and 8 mg/kg were administered three times at 4-week intervals to determine the optimum dose, the 8 mg/kg group had a ACR20 response rate of 78.2 %, showing high efficacy, and also from a pharmacokinetic standpoint, ≥ 1 $\mu\text{g/mL}$ of serum MRA concentrations at 4 weeks after the 3rd dose could be maintained in about 80% of the subjects. Therefore, it was determined that 8 mg/kg/4 wk is the appropriate recommended clinical dosage regimen. pJIA has a similar pathology to RA and it has been reported that an adequate effect can be obtained at a dosage regimen similar to that for RA also with existing therapeutic drugs and the therapeutic effectiveness of other IgG treatments for JIA has also been confirmed at a dosage regimen similar to that for RA. Therefore, similarly to RA, 8 mg/kg/4 wk was chosen as the recommended clinical dosage regimen and its appropriateness was confirmed based on the relationship between the serum MRA trough concentration and CRP etc. in phase III studies. On the other hand, for sJIA, studies for MCD and RA indicated that the serum MRA trough concentration required to normalize CRP is different among the different diseases and a higher MRA concentration is required for MCD in which serum IL-6 levels are very high, and it has been reported that IL-6 levels in synovial fluid are higher in sJIA compared to RA. Taking

account of these findings, a dosing interval of 2 weeks was selected, as with MCD, for an early phase II, ascending-dose study, and the dose was increased from 2 to 8 mg/kg according to individual levels of CRP in order to determine the optimal dose. As a result, there were subjects in whom decreased CRP could not be maintained at 4 mg/kg, while decreased CRP could be maintained in all subjects at 8 mg/kg. Thus, 8 mg/kg/2 wk was chosen as the recommended clinical dosage regimen.

The relationship between the serum MRA trough concentration and the CRP level obtained from clinical studies was compared among the different diseases. As shown in the following figure, the minimum effective blood concentration required to normalize CRP is around 1 µg/mL for RA, pJIA, and sJIA, respectively. It was indicated that the serum MRA trough concentrations observed in sJIA patients are well above the minimum effective blood concentration, however, the dose of concomitant corticosteroids was higher in sJIA patients compared to RA and pJIA patients, and taking account of the effects of corticosteroids on CRP levels, the possibility that the minimum effective blood MRA concentration for sJIA is underestimated can not be ruled out. In a sJIA study, even 8 mg/kg/2 wk could not maintain ≥ 1 µg/mL of serum MRA concentrations in about 10 % of the subjects (Study MRA316JP, 4 of 50 subjects at the end of Week 6), and furthermore, the disease is very serious, which may be complicated by macrophage activation syndrome (MAS) and a faster and reliable control of the disease condition is needed. Taking account of these points etc., 8 mg/kg/2 wk is considered a necessary and appropriate dosage regimen for sJIA.

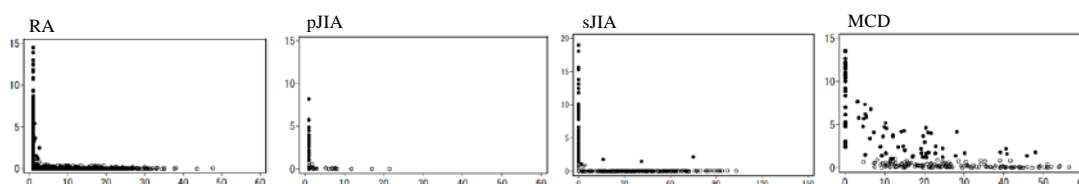


Figure. Serum MRA concentrations and CRP levels in different diseases
(X-axis, Serum MRA concentration [µg/mL]; Y-axis, CRP level [mg/dL])
●, CRP<1 mg/dL; ○, CRP>1 mg/dL

PMDA asked the applicant to explain the justification for determining that the minimum effective serum MRA concentration is 1 µg/mL for RA, pJIA (and sJIA), also in terms of the occupancy of IL-6R by MRA and IL-6, etc.

The applicant explained as follows:

Based on the results of an *in vitro* study of receptor occupancy during competitive inhibition (Attached document F-25 in the initial application), the minimum effective serum MRA

concentration when IL-6 was 100 pg/mL was calculated to be 0.93 µg/mL. Based on this figure, using the mean serum IL-6 levels after the first dose of MRA (4 weeks after the first dose for RA and pJIA, 2 weeks after the first dose for sJIA) in clinical studies for RA, pJIA and sJIA (88.97, 57.0, and 117.2 pg/mL, respectively, the 75 percentile was 117, 68.3, and 130.00 pg/mL, respectively), the MRA concentration required to inhibit IL-6 in each disease was calculated to be 0.7, 0.3, and 1.3 µg/mL, respectively (the 75 percentile was 1.3, 0.4, and 1.6 µg/mL, respectively). Therefore, it is appropriate to determine the dosage regimen with a view to maintaining serum MRA concentrations at ≥ 1 µg/mL for all the diseases.

PMDA asked the applicant to discuss the cause of lower serum MRA concentrations over time in pJIA patients than in RA patients and to provide a justification for choosing a dosing interval of 4 weeks for pJIA, as chosen for RA, taking into account that the proportion of patients who failed to achieve ≥ 1 µg/mL of serum MRA concentrations was higher in pJIA patients (about 40 %) compared to RA patients (about 15-20 %).

The applicant explained as follows:

In Study MRA318JP for pJIA, the patient background was compared between the subgroups with serum MRA concentrations < 1 µg/mL and ≥ 1 µg/mL after the 1st and 3rd doses of MRA. As a result, a trend towards failure to maintain serum MRA concentrations in patients with low height, with low body weight, and at young age was suggested, which is considered attributable to the possibility that clearance of MRA is increased in children due to a large liver volume per body weight. On the other hand, when the JIA core set response rate at the last observation (at 4 weeks after the 3rd dose) was compared between the subgroup with serum MRA concentrations ≥ 1 µg/mL throughout the study period and the subgroup with serum MRA concentrations < 1 µg/mL at any sampling point, the percentage of patients achieving a 70% improvement in the JIA core set tended to be lower in the subgroup with serum MRA concentrations < 1 µg/mL (40.0 %) compared to the subgroup with serum MRA concentrations ≥ 1 µg/mL (77.8 %) while the percentages of patients achieving 30% and 50% improvement in the JIA core set were high, i.e. ≥ 90 % in both subgroups and furthermore, it has been suggested that the efficacy in pJIA and RA is also similar [see “4.(iii).B.(1).2) Polyarticular-course juvenile idiopathic arthritis (pJIA)”]. Therefore, it is appropriate to choose a dosing interval of 4 weeks for pJIA, as with RA.

PMDA asked the applicant to explain the necessity of identifying the background factors common to the patients in whom serum MRA concentrations can not be maintained at ≥ 1 µg/mL also for sJIA and RA and including a caution about such factors in the package insert etc.

The applicant responded as follows:

As with pJIA patients, there is a trend in sJIA patients towards failure to maintain ≥ 1 $\mu\text{g/mL}$ of serum MRA concentrations in patients with low body weight, at young age, and with low height. Considering the seriousness of the disease, care needs to be taken so that the effective blood concentration is maintained especially in sJIA patients. Therefore, in order to call attention, it will be stated in the package insert that the elimination rate of MRA may be rapid in patients with any of these factors.

The applicant explained as follows:

In RA patients, the effects of sex, body weight, age, hepatic impairment, and renal impairment etc. on serum MRA trough concentrations were investigated. As a result, a subgroup of male patients with low body weight tended to have a low serum MRA concentration per body weight, which was within the interindividual variability in a subgroup of male patients with high body weight. Thus, a particular caution statement should be unnecessary.

PMDA largely accepts the above response. However, especially for pJIA and sJIA, due to very limited number of patients treated in clinical trials, it is necessary to confirm its appropriateness based on the efficacy and safety data etc. under routine drug uses via post-marketing surveillance etc. Since the possibility that body weight, height, and age etc. may affect the pharmacokinetics of MRA has been suggested, it is important to further investigate factors that may affect the efficacy and safety etc. of MRA including these factors and provide its information to the medical practice appropriately to ensure the proper use of MRA.

4.(ii).B.(2) Effects on metabolizing enzymes

Since a drug interaction study etc. has indicated that the expression levels of CYP2C19 and CYP3A4 etc. are increased following the administration of MRA in RA patients, PMDA asked the applicant to explain the effects of MRA on the pharmacokinetics of drugs that are metabolized by these CYPs and are expected to be used concomitantly with MRA.

The applicant explained as follows:

Concerning the concomitant drugs used in studies for adult RA patients (MRA009JP, MRA213JP, MRA012JP) and sJIA patients (MRA316JP), their doses before and after the administration of MRA were assessed. As a result, of the 5 subjects who received concomitant glibenclamide, which is metabolized by CYP3A4, the dose of glibenclamide was increased after the administration of MRA in 1 subject, but the dose was decreased in 1 subject and unchanged

in 3 subjects, showing no consistent trend. The doses of other concomitant drugs that are known to be metabolized by CYP3A4 and 2C19 etc. were not increased after the administration of MRA. Taking account of the results from the drug interaction study etc., a caution statement that the effects of concomitant drugs may be reduced following the administration of MRA will be included in the package insert.

PMDA considers as follows:

Since some of the drugs that are metabolized by CYP2C19 and CYP3A4 etc., which have been suggested to be affected by IL-6 signal, require careful adjustment of blood concentrations, it is necessary to further investigate the safety and efficacy of drugs that may be metabolized by these CYPs in combination with MRA, via post-marketing surveillance etc.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from a Japanese phase I/II study (MRA002JP), a Japanese phase II study (MRA009JP), Japanese phase III studies (MRA012JP, MRA213JP, and MRA318JP for pJIA patients) and Japanese extension studies (MRA003JP, MRA010JP) in RA patients, and a Japanese phase II study (MRA011JP) and a Japanese phase III study (MRA316JP) in sJIA patients were submitted. As the safety evaluation data, the results from a Japanese phase I study in healthy adults (MRA001JP) and Japanese clinical pharmacology studies in healthy adults and RA patients (MRA220JP, MRA221JP, and MRA004JP) were submitted. In the course of the regulatory review, the safety information based on the interim reports on the Japanese extension studies etc. was submitted.

4.(iii).A.(1) Phase I study (Attached document 5.3.3.1-1, MRA001JP [■■■ 19■■■ to ■■■ 19■■■])

A single-blind study in Japanese healthy male adults (target number of cases: 49) was conducted to investigate the safety of MRA, estimate the safe dose range, and determine its pharmacokinetics. Single intravenous doses of MRA were to be administered in 7 steps starting from the lowest dose (6 dose levels, 0.15-7.0 mg/kg) and the control group (the placebo group) was included in each step. Since the study population was healthy adults, the study was finished at 2.0 mg/kg (the 4th step) for ethical considerations. The observation period was 49 days after the start of study drug administration.

All of the 28 treated subjects (MRA groups, 20 subjects [5 subjects for each dose group]; placebo groups, 8 subjects) were included in the safety analysis.

Adverse events (including abnormal laboratory values) occurred in 71.4 % (20 of 28 subjects, 89 events). In the MRA groups, 45.0 % (9 of 20 subjects) experienced 36 adverse events for which a causal relationship to the study drug could not be denied (adverse drug reactions, including abnormal laboratory values) (0.5 mg/kg group, 2 subjects/22 events; 1.0 mg/kg group, 2 subjects/4 events; 2.0 mg/kg group, 5 subjects/10 events). The main events were IL-2 hyporesponsiveness (4 events), neutrophil count decreased (3 events), pharyngolaryngeal pain (2 events), cough (2 events), and rhinorrhoea (2 events) etc., but there were no deaths or serious events and none of the subjects were positive for anti-MRA antibodies. Though not assessed as an adverse event, serum complement titer decreased (CH50) suggestive of the pharmacological action of MRA was noted in 4 of 5 subjects in the MRA 2.0 mg/kg group.

Based on the above results, the applicant explained that although the administration of MRA may lower the body's resistance to infections, it was judged that there are no major safety problems.

4.(iii).A.(2) Clinical pharmacology studies

4.(iii).A.(2).1) Study to investigate the effects on ECGs and safety (Attached document 5.3.3.1-2, MRA004JP [■■■ 19■■■ to ■■■ 19■■■])

An open-label study in Japanese healthy male adults (target number of cases: 6) was conducted to investigate the effects of MRA on ECGs and the safety. A single intravenous dose of MRA 2 mg/kg was to be administered. The ECG was measured continuously until the following day of MRA administration, to be compared to the ECG obtained on the day before administration (saline was administered as the control). The observation period was 4 weeks including a follow-up examination.

All of the 6 treated subjects were included in the safety analysis.

There were no clinically relevant abnormal changes/abnormal findings in the ECG throughout the observation period in any subject.

Adverse events (including abnormal laboratory values) occurred in 100.0 % (6 of 6 subjects, 30 events). Adverse drug reactions (including abnormal laboratory values) were reported by 6 subjects (13 events). The main events were white blood cell count decreased (6 subjects), blood fibrinogen decreased (6 subjects), and neutrophil count decreased (1 subject), but there were no deaths or serious events and none of the subjects were positive for anti-MRA antibodies.

4.(iii).A.(2).2) Drug interaction study in RA patients (Attached document 5.3.3.4-1, MRA220JP[■■■ 20■■■ to ■■■ 20■■■])

An open-label study in Japanese RA patients (target number of cases: CYP3A4 group, 13; CYP2C19-PM group, 5; CYP2C19-EM group, 13) was conducted to investigate the effects of the inhibition of IL-6 signal transduction by MRA on drug-metabolizing enzymes (CYP3A4 and CYP2C19) and the safety and efficacy of MRA. Dextromethorphan hydrobromide 30 mg (CYP3A4 group) or omeprazole 10 mg (CYP2C19-PM group and CYP2C19-EM group) was orally administered on Day 0 and Day 14 and a single intravenous dose of MRA 8 mg/kg was administered on Day 7. The observation period was 42 ± 2 days.

All of the 31 treated subjects (CYP3A4 group, 13 subjects; CYP2C19-PM group, 5 subjects; CYP2C19-EM group, 13 subjects) were included in the safety and efficacy analyses.

Adverse events (including abnormal laboratory values) occurred in 67.7 % (21 of 31 subjects, 36 events) (CYP3A4 group, 76.9 % [10 of 13 subjects, 21 events]; CYP2C19-PM group, 80.0 % [4 of 5 subjects, 6 events]; CYP2C19-EM group, 53.8 % [7 of 13 subjects, 9 events]). Adverse drug reactions (including abnormal laboratory values) occurred in 48.4 % (15 of 31 subjects, 20 events) (CYP3A4 group, 69.2 % [9 of 13 subjects, 12 events]; CYP2C19-PM group, 60.0 % [3 of 5 subjects, 4 events]; CYP2C19-EM group, 23.1 % [3 of 13 subjects, 4 events]). The main events were white blood cell count decreased and stomatitis (3 subjects each), and bronchitis, influenza, nasopharyngitis, tinea pedis, positional dizziness, angina pectoris, peripheral vascular disorder, gastritis, eczema, purpura, urticaria, ALT increased, AST increased, and glucose urine present (one subject each). There were no deaths or serious events.

The percentage of ACR20 responders on the last observation day was 92.3 % (12 of 13 subjects) in the CYP3A4 group, 80.0 % (4 of 5 subjects) in the CYP2C19-PM group, and 84.6 % (11 of 13 subjects) in the CYP2C19-EM group.

4.(iii).A.(2).3) Pharmacokinetic and safety study in RA patients with renal impairment (Attached document 5.3.3.3-1, MRA221JP [■■■ 20■■■ to ■■■ 20■■■])

An open-label study in Japanese RA patients with renal impairment (the degree of renal impairment was classified according to the mean creatinine clearance [CrCL]: mild, $50 < \text{CrCL} \leq 80$; moderate, $30 < \text{CrCL} \leq 50$; severe, $10 < \text{CrCL} \leq 30$) (target number of cases: mild, ≥ 4 subjects; moderate, ≥ 4 subjects; severe, unspecified; A total of ≥ 10 subjects) was conducted to investigate the pharmacokinetics and safety of MRA. A single intravenous dose of MRA 8

mg/kg was to be administered and the observation period was 35 days.

All of the 14 treated subjects (mild: 4 subjects, moderate: 5 subjects, severe: 3 subjects, Non-renal impairment²: 2 subjects) were included in the efficacy and safety analyses.

Adverse events (including abnormal laboratory values) occurred in 92.9 % (13 of 14 subjects, 29 events) (mild, 100.0 % [4 of 4 subjects, 11 events]; moderate, 100.0 % [5 of 5 subjects, 13 events]; severe, 100.0 % [3 of 3 subjects, 4 events]; Non-renal impairment, 50.0 % [1 of 2 subjects, 1 event]). Adverse drug reactions (including abnormal laboratory values) occurred in 64.3 % (9 of 14 subjects, 18 events) (mild, 4 of 4 subjects; moderate, 60.0 % [3 of 5 subjects]; severe, 66.7 % [2 of 3 subjects]; Non-renal impairment, 0 % [0 of 2 subjects]). The most common System Organ Classes of the events reported were “Investigations” (7 subjects, 9 events) (including 2 events of blood triglycerides increased), “Skin and subcutaneous tissue disorders” (2 subjects, 3 events), and “Infections and infestations” (2 subjects, 2 events) etc. Serious adverse drug reactions were noted in one subject with moderate renal impairment (skin ulcer and peripheral neuropathy) and the outcome of skin ulcer was reported as “recovered/resolved” and the outcome of peripheral neuropathy was reported as “recovering/resolving.” There were no deaths.

Infusion reactions reported were hypoesthesia (1 subject with mild renal impairment) and drug eruption (1 subject with moderate renal impairment), but none of the subjects were positive for anti-MRA antibodies and there were no clinically relevant changes in vital signs or ECGs.

The primary efficacy endpoint, i.e. the percentage of ACR20 responders 28 days post-dose was 28.6 % (4 of 14 subjects) (mild, 25.0 % [1 of 4 subjects]; moderate, 20.0 % [1 of 5 subjects]; severe, 33.3 % [1 of 3 subjects]; Non-renal impairment, 50.0 % [1 of 2 subjects]).

4.(iii).A.(3) Phase I/II study in RA patients (Attached document 5.3.5.2-RA-1, MRA002JP [■ 19■ to ■ 20■])

An open-label study in Japanese RA patients (target number of cases: 5 cases per group, total 15 cases) was conducted to evaluate the safety, pharmacokinetics, and efficacy of MRA. Subjects were to receive three intravenous doses of MRA 2 mg/kg, 4 mg/kg, or 8 mg/kg (assigned in the order of enrollment) at 2-week intervals. The study was started with the low dose group and if it was judged that there were no problems with the safety up to 2 weeks after the 3rd dose, the decision to move to the next dose level was made. In each group, if there were no problems with

² These subjects had CrCL_≤80 mL/min at the time of enrollment, meeting the inclusion criteria, but the mean of two CrCL measurements obtained during hospitalization exceeded 80 mL/min.

the safety up to 2 weeks after the 3rd dose and the CRP or ESR was improved, the subject was allowed to adjust the dosing interval (2-4 weeks) as appropriate and continue treatment for up to 24 weeks after the 1st dose.

All of the 15 treated subjects were included in the safety and efficacy analyses.

Adverse events (including abnormal laboratory values) occurred in 100.0 % (15 of 15 subjects, 132 events) (2 mg/kg group, 5 of 5 subjects [55 events]; 4 mg/kg group, 5 of 5 subjects [51 events]; 8 mg/kg group, 5 of 5 subjects [26 events]). Adverse drug reactions (including abnormal laboratory values) occurred in 14 of 15 subjects (70 events) (2 mg/kg group, 5 of 5 subjects [37 events]; 4 mg/kg group, 5 of 5 subjects [20 events]; 8 mg/kg group, 4 of 5 subjects [13 events]) and the main events were blood cholesterol increased (10 events), low density lipoprotein increased (7 events), blood lactate dehydrogenase increased (4 events), iron metabolism disorder (4 events), blood triglycerides increased (3 events), blood glucose increased (3 events), blood urea increased (3 events), pyrexia (2 events), nasopharyngitis (2 events), and white blood cell count decreased (2 events), etc. The incidence of each event was not dose-dependent and all events were mild or moderate in severity. A serious adverse event of herpes zoster was noted in the 2 mg/kg group, but its causal relationship to the study drug was denied. No deaths occurred. None of the subjects were positive for anti-MRA antibodies and there were no clinically relevant changes in vital signs or ECGs.

The primary efficacy endpoint, i.e. the time courses of CRP and ESR up to the end of Week 6 are as shown in the following figure. The change and percent change from baseline to the end of Week 6 in CRP (mean \pm SD) were -5.36 ± 5.40 mg/dL and $-78.1 \pm 46.3\%$, respectively, in the 2 mg/kg group ($p=0.091$ and $p=0.020$, paired t-test), -4.05 ± 2.22 mg/dL and $-81.3 \pm 30.8\%$, respectively, in the 4 mg/kg group ($p=0.015$ and $p=0.004$, paired t-test), and -5.40 ± 1.72 mg/dL and $-99.4 \pm 0.2\%$, respectively, in the 8 mg/kg group ($p=0.002$ and $p<0.001$, paired t-test), and although significant reductions were noted in all groups except for the change from baseline in the 2 mg/kg group, no dose response was observed ($p=0.492$ and $p=0.081$, Jonckheere test). In 3 subjects with serum MRA concentrations below the lower limit of quantification (1 μ g/mL) (1 subject in the 2 mg/kg group, 2 subjects in the 4 mg/kg group), the CRP did not become negative during the study period. The change and percent change from baseline to Week 6 in ESR were -59.8 ± 19.4 mm/hr and $-66.6 \pm 18.8\%$, respectively, in the 2 mg/kg group ($p=0.002$ and $p=0.001$, paired t-test), -57.0 ± 12.0 mm/hr and $-66.5 \pm 21.2\%$, respectively, in the 4 mg/kg group ($p<0.001$ and $p=0.002$, paired t-test), and -61.1 ± 18.4 mm/hr and $-80.8 \pm 2.7\%$, respectively, in the 8 mg/kg group ($p=0.002$ and $p<0.001$, paired t-test), and although significant

reductions were noted in all groups, no dose response was observed, as with CRP ($p=0.751$ and $p=0.316$, Jonckheere test).

Based on the above, the applicant explained that the tolerability of repeated doses of MRA 8 mg/kg every 2 weeks in RA patients has been confirmed and the efficacy of MRA has been suggested.

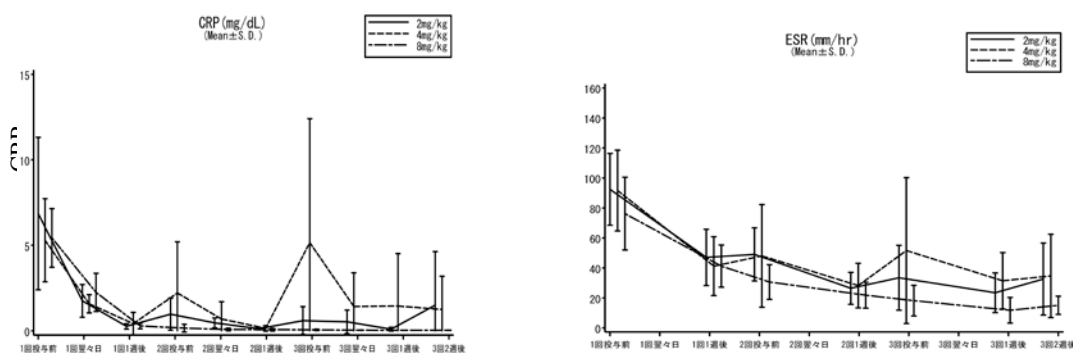


Figure. Time courses of CRP and ESR up to Week 6

Timepoints (from left to right on the horizontal axis in the both figures): pre-1st dose, 2 days after 1st dose, 1 week after 1st dose, pre-2nd dose, 2 days after 2nd dose, 1 week after 2nd dose, pre-3rd dose, 2 days after 3rd dose, 1 week after 3rd dose, 2 weeks after 3rd dose

4.(iii).A.(4) Late phase II study in RA patients (Attached document 5.3.5.1-RA-1, MRA009JP [2020 to 2020])

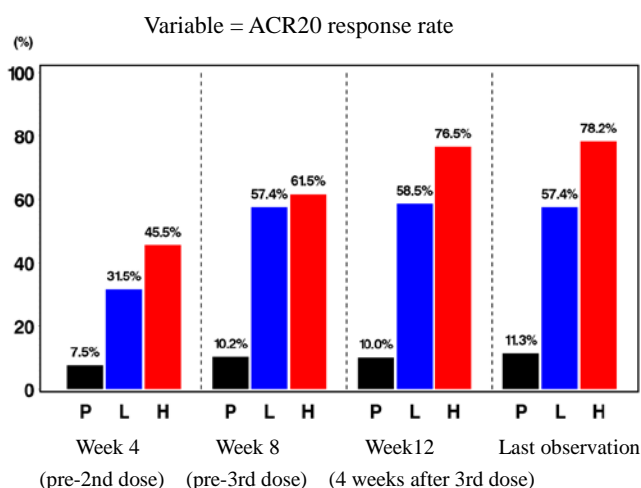
A randomized, placebo-controlled, double-blind, parallel-group, comparative study in Japanese RA patients (target number of cases: 45 cases per group, total 135 cases) was conducted to determine the optimum dose of MRA. Subjects were to receive three intravenous doses of MRA 4 mg/kg (L group), 8 mg/kg (H group), or placebo (P group) at 4-week intervals and the overall treatment period was 3 months including a 1-month follow up after the last dose.

A total of 164 patients were enrolled into the study (L group, 55 subjects; H group, 55 subjects; P group, 54 subjects), 163 subjects excluding 1 untreated subject (L group, 54 subjects; H group, 55 subjects; P group, 54 subjects) were included in the safety analysis, among which, 162 subjects excluding 1 subject who had received corticosteroids within 4 weeks prior to study treatment (L group, 54 subjects; H group, 55 subjects; P group, 53 subjects) were included in the FAS (Full Analysis Set) for efficacy, and furthermore, 153 subjects excluding a total of 9

subjects, i.e. 3 subjects with protocol violations and 6 prematurely discontinued subjects (L group, 54 subjects; H group, 51 subjects; P group, 48 subjects), were included in the PPS (Per Protocol Set).

The primary endpoint, i.e. the percentage of ACR20 responders³ on the last observation day in the FAS was 78.2 % (43 of 55 subjects) in the H group, 57.4 % (31 of 54 subjects) in the L group, and 11.3 % (6 of 53 subjects) in the P group and significant improvement was observed in the H group compared to the P group ($p < 0.001$, χ^2 test). Also, significant improvement was observed in the L group compared to the P group and in the H group compared to the L group, respectively (P group vs. L group, $p < 0.001$; L group vs. H group, $p = 0.020$, χ^2 test).

Concerning the time course of the percentages of ACR20, ACR50, and ACR70 responders, i.e. secondary endpoints, the percentage of ACR20 responders was significantly higher in both the H group and L group compared to the P group from Week 4 onwards (H group, $p < 0.001$; L group, $p = 0.002$; χ^2 test, see the figure on the right). The percentage of ACR50 responders and the percentage of ACR70 responders were significantly higher in the H group compared to the P group



from Week 8 onwards (ACR50 response rate, $p < 0.001$; ACR70 response rate, $p = 0.008$; χ^2 test). Also in the L group, the percentage of ACR50

Figure. ACR20 response rates on the last observation day

responders was significantly higher compared to the P group from Week 8 onwards ($p = 0.002$, χ^2 test) and the percentage of ACR70 responders was significantly higher compared to the P group from Week 12 onwards ($p = 0.007$). As to the time course of DAS28⁴ (Modified Disease Activity

³ The criteria defined by the American College of Rheumatology. ACR20 response criteria are defined as at least a 20% reduction in tender joint count and swollen joint count plus at least a 20% improvement in at least three of the remaining five activity measures: 1. Patient's assessment of pain, 2. Patient's global assessment of disease activity, 3. Physician's global assessment of disease activity, 4. MHAQ, 5. CRP or ESR. ACR50 and ACR70 response criteria are defined as 50% and 70% improvements, respectively, in these measures.

⁴ DAS28 score is calculated according to the following formula, using the number of tender joints of the 28 assessed (tenderness or pain on motion) (TJC), the number of swollen joints of the 28 assessed (SJC), ESR, and the patient's general health (GH). $DAS28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.7\ln ESR + 0.014 \times GH$

Score on 28 Joint Counts) up to the last observation day, there were significant differences for all comparisons of P group vs. H group, P group vs. L group, and L group vs. H group from Week 4 onwards.

Adverse events (including abnormal laboratory changes) occurred in 89.1 % (49 of 55 subjects, 205 events) in the H group, 81.5 % (44 of 54 subjects, 128 events) in the L group, and 72.2 % (39 of 54 subjects, 89 events) in the P group. Serious adverse events reported were one death due to Epstein-Barr (EB) virus reactivation and allergic alveolitis (1 subject) in the H group and secondary infection NOS (1 subject) in the L group, which were all classified as adverse drug reactions. In the P group, 1 subject had subarachnoid haemorrhage NOS and 1 subject had femur fracture, but a causal relationship to the study drug was denied for both cases.

Adverse drug reactions (including abnormal laboratory changes) occurred in 85.5 % (47 of 55 subjects, 166 events) in the H group, 72.2 % (39 of 54 subjects, 85 events) in the L group, and 48.1 % (26 of 54 subjects, 49 events) in the P group and the main events (excluding abnormal laboratory changes) were nasopharyngitis (H group, 3 subjects; L group, 5 subjects; P group, 3 subjects), hypercholesterolaemia (H group, 3 subjects; L group, 2 subjects; P group, 0 subject), and pyrexia (H group, 3 subjects; L group, 1 subject; P group, 1 subject) etc. The main abnormal laboratory findings were blood cholesterol increased (H group, 27 subjects; L group, 15 subjects; P group, 2 subjects), blood triglycerides increased (H group, 8 subjects; L group, 7 subjects; P group, 3 subjects), gamma-glutamyltransferase (γ -GTP) increased (H group, 7 subjects; L group, 1 subject; P group, 1 subject), high density lipoprotein increased (H group, 5 subjects; L group, 3 subjects; P group, 1 subject), and white blood cell count decreased (H group, 5 subjects; L group, 4 subjects; P group, 0 subject), etc.

An infusion reaction was defined as an adverse event occurring during an infusion of MRA or post-infusion on the day of infusion. The incidence of infusion reactions was 16.4 % (9 of 55 subjects) in the H group, 13.0 % (7 of 54 subjects) in the L group, and 18.5 % (10 of 54 subjects) in the P group and the incidence of infusion reactions classified as adverse drug reactions was 12.7 % (7 of 55 subjects) in the H group, 3.7 % (2 of 54 subjects) in the L group, and 11.1 % (6 of 54 subjects) in the P group, but there were no serious cases and 3 cases in the H group (1 case of feeling of ear closed/malaise/hypertension NOS, 1 case of blood pressure increased, 1 case of blood pressure decreased), 2 cases in the L group (1 case of cough/sputum increased, 1 case of eruption), and 2 cases in the P group (2 cases of blood pressure increased) were rated as moderate and the other cases were all rated as mild.

Anti-MRA antibodies were detected in 1 subject each in the H group, the L group, and the P group and these subjects were discontinued from study treatment according to the protocol-specified withdrawal criteria. As a result of reassessment, 1 subject in the H group and 1 subject in the L group were determined to be positive for IgE antibodies and 1 subject in the P group was determined to be negative, and there were no neutralizing antibody-positive subjects. Events such as anaphylactic shock due to the development of antibodies were not observed.

Adverse events leading to treatment discontinuation were reported in 2 subjects in the H group (EB virus reactivation and white blood cell decreased) and 4 subjects in the P group (peripheral swelling, road traffic accident, femoral neck fracture, and itching NOS/palpitations/urinary occult blood positive, one subject each), of which the EB virus reactivation and the white blood cell decreased in the H group and the itching NOS/palpitations/urinary occult blood positive in the P group were classified as adverse drug reactions.

Based on the above, the applicant explained that as the efficacy of MRA in RA was higher in the 8 mg/kg group compared to the 4 mg/kg group and the tolerability of MRA up to 8 mg/kg has been confirmed, the recommended clinical dose should be 8 mg/kg (every-4-week administration).

4.(iii).A.(5) Phase III study in RA patients (Attached document 5.3.5.1-RA-5, MRA012JP [■■■ 20■■■ to ■■■ 20■■■])

A randomized, open-label, parallel-group, comparative study using conventional therapies as a control was conducted in Japanese patients with RA of a certain disease activity⁵ despite prior or current therapy with at least one disease modifying anti-rheumatic drug (DMARD) or immunosuppressant, to confirm the effect of MRA in delaying the progression of bone/joint destruction and the safety of a long-term treatment with MRA (target number of cases: 150 cases per group, total 300 cases). The MRA group was to receive 8 mg/kg of intravenous MRA every 4 weeks and the control group was to receive drugs intended for the treatment of RA (excluding infliximab, etanercept, and leflunomide etc., which have been shown to delay the progression of bone/joint destruction in foreign clinical trials etc.) as prescribed appropriately though no restrictions were imposed on the dose. The duration of treatment was 52 weeks. In the MRA group, the concomitant use of DMARDs and immunosuppressants besides infliximab, etanercept, and leflunomide etc. was prohibited. The concomitant use of bisphosphonates was

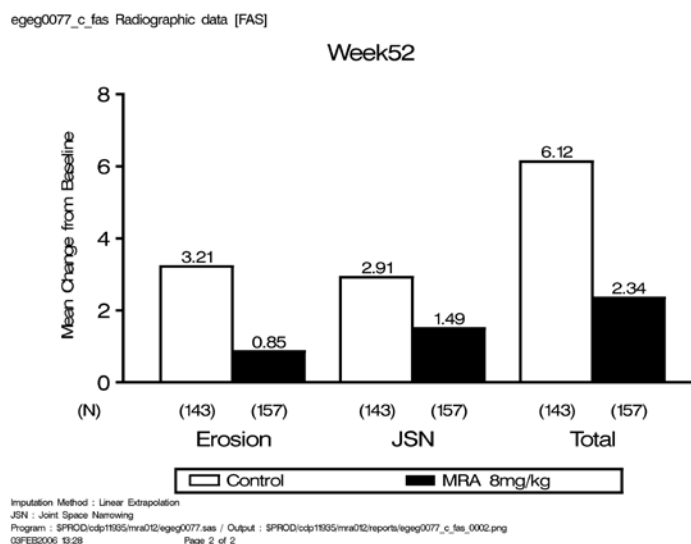
⁵ Patients were eligible if all of the following three conditions were met at the time of enrollment (within 2 weeks prior to study drug administration): (1) at least 6 tender joints (pain on motion or tenderness) of the 49 joints as listed in the criteria 1) of the Drug Evaluation Committee of the Japan Rheumatism Foundation, (2) at least 6 inflamed, swollen joints of the 46 joints as listed in the criteria 1) of the Drug Evaluation Committee of the Japan Rheumatism Foundation, (3) ESR (Westergren method) ≥ 30 mm/hr and CRP ≥ 2.0 mg/dL.

prohibited in both groups because they may have an inhibitory effect on bone/joint destruction based on the findings from patients with multiple myeloma or bone metastases from breast cancer. As to the use of oral corticosteroids (≤ 10 mg/day of prednisolone equivalents), adjustments in the dose were allowed with no restrictions on the dose in the control group and with the dose at the start of MRA treatment being the upper limit in the MRA group.

A total of 306 patients were enrolled into the study (control group, 148 subjects; MRA group, 158 subjects), 302 subjects excluding 3 subjects who were withdrawn before the initial observation in the control group and 1 subject who was withdrawn before the administration of MRA in the MRA group (control group, 145 subjects; MRA group, 157 subjects) were included in the FAS for safety and efficacy, and 290 subjects excluding 8 subjects who were prematurely discontinued from the study drug, 4 subjects with major violations as to the inclusion/exclusion criteria (One of them was also a prematurely discontinued subject), and 1 subject who used a prohibited concomitant drug (control group, 139 subjects; MRA group, 151 subjects) were included in the PPS.

The primary endpoint, i.e. the mean change (median) in the modified Sharp erosion score at 52 weeks post-dose⁶ in the FAS was 3.21 (1.0) in the control group and 0.85 (0.0) in the MRA group (baseline score: 14.10 ± 21.78 in the control group, 13.83 ± 24.59 in the MRA group), which demonstrated significant inhibition of the progression of bone erosion ($p < 0.001$, analysis of covariance including baseline

score and disease duration as covariates,⁷ see the figure on the right). There was a significant between-treatment difference when the missing values were imputed using LOCF (last observation carried forward) and when the missing values were not imputed, as well as when the missing values were imputed by



linear extrapolation.

Figure. Change in erosion score etc. at 52 weeks post-dose

Regarding the secondary endpoints, the mean change (median) in the modified Sharp joint space

⁶ If the data at 52 weeks post-dose were missing, the missing data were to be imputed by linear extrapolation, and blinded radiological assessment was performed.

⁷ The criterion variable and covariates were rank-transformed.

narrowing score at 52 weeks post-dose was 2.91 (1.0) in the control group and 1.49 (0.0) in the MRA group and the mean change (median) in the total Sharp score at 52 weeks post-dose was 6.12 (2.5) in the control group and 2.34 (0.5) in the MRA group, which also showed significant between-treatment differences ($p=0.024$ and $p=0.001$, respectively, analysis of covariance including baseline score and disease duration as covariates⁷). The percentage of ACR20 responders at the last observation was 35.2 % (50 of 142 subjects) in the control group and 89.2 % (140 of 157 subjects) in the MRA group, the percentage of ACR50 responders was 14.1 % (20 of 142 subjects) in the control group and 71.3 % (112 of 157 subjects) in the MRA group, and the percentage of ACR70 responders was 5.6 % (8 of 142 subjects) in the control group and 46.5 % (73 of 157 subjects) in the MRA group, which all showed significant improvement ($p<0.001$ for all, χ^2 test). The change in DAS28 score (mean \pm SD) at the last observation was -0.978 ± 1.318 in the control group and -4.026 ± 1.312 in the MRA group, which also showed significant improvement ($p<0.001$, Student's t test).

Adverse events (including abnormal laboratory changes) occurred in 86.9 % (126 of 145 subjects, 439 events) in the control group and 95.5 % (150 of 157 subjects, 754 events) in the MRA group and serious adverse events were reported in 13.1 % (19 of 145 subjects, 32 events) in the control group and 18.5 % (29 of 157 subjects, 30 events) in the MRA group. Although 18 serious adverse drug reactions occurred in the MRA group (17 subjects) (cellulitis, pneumonia, and pleurisy [2 events each], epiglottitis, gastroenteritis, herpes zoster, infection, perianal abscess, bacterial pneumonia, breast cancer, breast cancer in situ, colon cancer, ventricular tachycardia, gastritis, and hepatic function abnormal [1 event each]), the outcomes of these adverse drug reactions were reported as "recovered/resolved" or "recovering/resolving." No deaths occurred in the control group or the MRA group. The main adverse events (excluding abnormal laboratory changes) were nasopharyngitis (MRA group, 35.7 % [56 subjects]; control group, 32.4 % [47 subjects]), rash (MRA group, 10.8 % [17 subjects]; control group, 4.1 % [6 subjects]), diarrhoea (MRA group, 8.3 % [13 subjects]; control group, 9.0 % [13 subjects]), and headache (MRA group, 7.0 % [11 subjects]; control group, 2.1 % [3 subjects]) etc. The main abnormal laboratory findings were blood cholesterol increased (MRA group, 38.2 % [60 subjects]; control group, 4.1% [6 subjects]), low density lipoprotein increased (MRA group, 26.1 % [41 subjects]; control group, 2.8 % [4 subjects]), blood triglycerides increased (MRA group, 16.6 % [26 subjects]; control group, 2.8 % [4 subjects]), ALT increased (MRA group, 12.7 % [20 subjects]; control group, 9.7 % [14 subjects]), and AST increased (MRA group, 10.8 % [17 subjects]; control group, 7.6 % [11 subjects]) etc.

Adverse drug reactions associated with MRA (including abnormal laboratory changes) occurred in 88.5 % (139 of 157 subjects, 540 events) in the MRA group,⁸ and the main events (excluding abnormal laboratory changes) were nasopharyngitis (29.9 %, 47 subjects), diarrhoea (7.0 %, 11 subjects), rash (5.7 %, 9 subjects), and paronychia (5.7 %, 9 subjects) and the main abnormal laboratory findings were blood cholesterol increased (38.2 %, 60 subjects), low density lipoprotein increased (26.1 %, 41 subjects), blood triglycerides increased (12.7 %, 20 subjects), ALT increased (10.8 %, 17 subjects), AST increased (8.9 %, 14 subjects), γ -GTP increased (7.0 %, 11 subjects), neutrophil count decreased (6.4 %, 10 subjects), and white blood cell count decreased (6.4 %, 10 subjects).

The incidence of infusion reactions in the MRA group was 7.6 % (12 of 157 subjects, 21 events) and the incidence of infusion reactions classified as adverse drug reactions was 7.0 % (11 of 157 subjects, 14 events) (headache, nausea, rash, injection site erythema, and blood pressure increased [2 subjects each], vomiting, hypertension, pruritus, and malaise [1 subject each]). Headache and chest pain were rated as moderate in severity, but other events were mild in severity.

Adverse events leading to treatment discontinuation were reported in 5 subjects in the control group (spinal compression fracture [2 events], femoral neck fracture, bone density decreased, and tendon rupture [1 event each]) and in 17 subjects in the MRA group (pneumonia, ventricular tachycardia, and pleurisy [2 events each], gastritis, rash, extrasystoles, depressed level of consciousness, γ -GTP increased, ALT increased, AST increased, breast cancer, infection, asthma, colon cancer, cellulitis, electrocardiogram T wave inversion, electrocardiogram T wave amplitude decreased, hepatic function abnormal, rheumatoid lung, and perianal abscess [1 event each]), which were all classified as adverse drug reactions except for 1 event of ventricular tachycardia, extrasystoles, depressed level of consciousness, asthma, and rheumatoid lung in the MRA group.

With respect to anti-MRA antibodies, IgE antibodies were detected in 4 subjects in the MRA group, but there were no neutralizing antibody-positive subjects. Two of these four subjects had infusion reactions (headache/tremor/nausea/vomiting/rash/chest pain/feeling cold in 1 subject, blood pressure increased in 1 subject).

Based on the above, the applicant explained that treatment with MRA has significantly inhibited the progression of bone/joint destruction and achieved ACR responses and the safety of MRA is

⁸ Causality assessment was not performed for the control group.

also considered acceptable.

4.(iii).A.(6) Methotrexate-controlled, phase III study in RA patients (Attached document 5.3.5.1-RA-4, MRA213JP [■■■ 20■■■ to ■■■ 20■■■])

A randomized, double-blind, parallel-group, methotrexate (MTX) 8 mg/week (MTX group)-controlled, comparative study in Japanese patients with RA of a certain disease activity⁹ on MTX 8 mg/week (target number of cases: 60 cases per group, total 120 cases) was conducted to evaluate the efficacy and safety of MRA. Subjects were to receive 8 mg/kg of intravenous MRA every 4 weeks or 8 mg of oral MTX once weekly for 24 weeks using the double dummy method.

A total of 127 patients were enrolled into the study (MTX group, 66 subjects; MRA group, 61 subjects), 125 subjects excluding 2 subjects who were withdrawn before the administration of study drug in the MTX group (MTX group, 64 subjects; MRA group, 61 subjects) were included in the safety analysis and in the FAS for efficacy, and 117 subjects excluding 1 subject with MTX non-compliance, 5 subjects who received an insufficient number of doses of study drug, and 3 subjects with major violations as to the inclusion/exclusion criteria (One of them was also a subject who received an insufficient number of doses) (MTX group, 58 subjects; MRA group, 59 subjects) were included in the PPS.

The primary endpoint, i.e. the percentage of ACR20 responders on the last observation day in the FAS was 25.0 % (16 of 64 subjects) in the MTX group and 80.3 % (49 of 61 subjects) in the MRA group, which showed a significant between-treatment difference ($p < 0.001$, χ^2 test). As to secondary endpoints, the percentage of ACR50 responders was 10.9 % (7 of 64 subjects) in the MTX group and 49.2 % (30 of 61 subjects) in the MRA group and the percentage of ACR70 responders was 6.3 % (4 of 64 subjects) in the MTX group and 29.5 % (18 of 61 subjects) in the MRA group, which both showed a significant between-treatment difference (ACR50 response rate: $p < 0.001$, ACR70 response rate: $p < 0.001$, χ^2 test, see the figure below).

⁹ Patients were eligible if all of the following three conditions were met at the time of enrollment (within 2 weeks prior to the start of study drug administration): (1) at least 6 tender joints (pain on motion or tenderness) of the 49 joints as listed in the criteria of the Drug Evaluation Committee of the Japan Rheumatism Foundation, (2) at least 6 inflamed, swollen joints of the 46 joints as listed in the criteria of the Drug Evaluation Committee of the Japan Rheumatism Foundation, (3) ESR (Westergren method) ≥ 30 mm/hr or CRP ≥ 1.0 mg/dL.

With respect to the time course of DAS28 up to the last observation day, a secondary endpoint, the DAS28 scores were lower in the MRA group than in the MTX group at all timepoints from Week 4 onwards. The change in DAS28 score (mean \pm SD) on the last observation day was -0.693 ± 1.258 in the MTX group and -3.182 ± 1.270 in the MRA group, which showed significant improvement in the MRA group ($p < 0.001$, Student's t test). Adverse

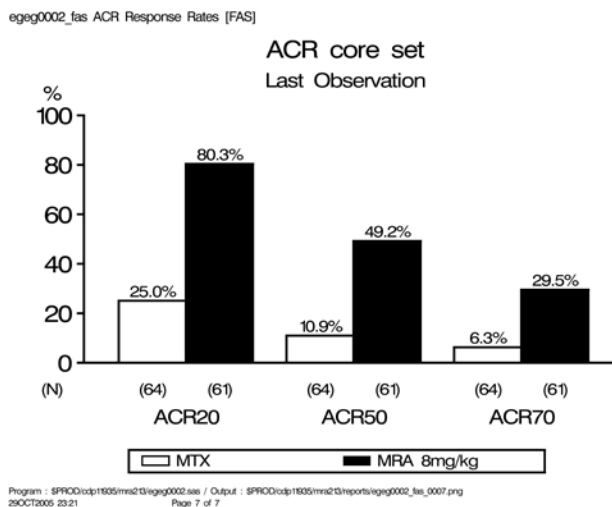


Figure. ACR response rates on the last observation day

events (including abnormal laboratory changes) occurred in 71.9 % (46 of 64 subjects) in the MTX group and 91.8 % (56 of 61 subjects) in the MRA group. Serious adverse events were observed in 4.7 % of the MTX group (3 of 64 subjects: pneumonia, spinal compression fracture, and femoral neck fracture, one case each) and 6.6 % of the MRA group (4 of 61 subjects: pneumonia, infective arthritis, colonic polyp, and headache, one case each), of which, pneumonia in the MTX group and pneumonia and infective arthritis in the MRA group were classified as adverse drug reactions and the outcome of pneumonia in both the MRA group and the MTX group was reported as “recovered/resolved” and the outcome of infective arthritis in the MRA group was reported as “recovering/resolving.” There were no deaths.

Adverse drug reactions were reported in 57.8 % (37 of 64 subjects, 74 events) in the MTX group and 82.0 % (50 of 61 subjects, 150 events) in the MRA group and the main events (excluding abnormal laboratory values) were nasopharyngitis (MTX group, 6 of 64 subjects; MRA group, 7 of 61 subjects), stomatitis (MTX group, 0 of 64 subjects; MRA group, 5 of 61 subjects), upper respiratory tract inflammation (MTX group, 3 of 64 subjects; MRA group, 2 of 61 subjects), hyperlipidaemia (MTX group, 0 of 64 subjects; MRA group, 4 of 61 subjects), headache (MTX group, 2 of 64 subjects; MRA group, 2 of 61 subjects), and pruritus (MTX group, 1 of 64 subjects; MRA group, 3 of 61 subjects). The main abnormal laboratory findings were blood cholesterol increased (MTX group, 2 of 64 subjects; MRA group, 22 of 61 subjects), low density lipoprotein increased (MTX group, 2 of 64 subjects; MRA group, 17 of 61 subjects), blood triglycerides increased (MTX group, 1 of 64 subjects; MRA group, 10 of 61 subjects), blood lactate dehydrogenase increased (MTX group, 3 of 64 subjects; MRA group, 4 of 61 subjects), and high density lipoprotein increased (MTX group, 2 of 64 subjects; MRA group, 4 of 61 subjects).

The incidence of infusion reactions was 14.8 % (9 of 61 subjects) in the MRA group and 6.3 % (4 of 64 subjects) in the MTX group and the incidence of infusion reactions classified as adverse drug reactions was 11.5 % (7 of 61 subjects, 8 events: pruritus [2 subjects], headache, flushing, rash, arthralgia, and feeling abnormal/blood pressure increased [1 subject each]) in the MRA group and 4.7 % (3 of 64 subjects, 3 events: hypersensitivity, pruritus, and pyrexia [1 subject each]) in the MTX group. Arthralgia in the MRA group was rated as moderate in severity while other events were mild in severity.

In this study, the development of anti-MRA antibodies was not detected.

Adverse events leading to treatment discontinuation were reported in 3 subjects in the MTX group (generalized urticaria, pneumonia, femoral neck fracture) and 2 subjects in the MRA group (pneumonia, infective arthritis) and all of these events except for the femoral neck fracture were classified as adverse drug reactions.

Based on the above, the applicant explained that the efficacy of MRA in patients with RA of a certain disease activity on MTX has been confirmed in a double-blind study and the safety of MRA is also considered acceptable.

4.(iii).A.(7) Phase III study in pJIA patients (Attached document 5.3.5.2-RA-2, MRA318JP [■■■ 20■■■ to ■■■ 20■■■])

An open-label, uncontrolled study in Japanese patients with polyarticular-course¹⁰ juvenile idiopathic arthritis (pJIA) aged at least 2 years old and less than 20 (under 16 years of age at onset) (target number of cases: 15) was conducted to evaluate the efficacy, safety, and pharmacokinetics of MRA. Subjects were to receive 3 intravenous doses of MRA 8 mg/kg at 4-week intervals and the treatment period was 12 weeks.

All of the 19 treated subjects were included in the safety analysis and in the FAS for efficacy and 17 subjects excluding a total of 2 subjects, i.e. 1 subject with violations as to the inclusion/exclusion criteria and 1 subject with violations as to concomitant medications, were included in the PPS.

The primary endpoint, i.e. the percentage of subjects showing 30% improvement in the JIA core

¹⁰ Patients were eligible if all of the following three conditions were met at the time of enrollment (within 2 weeks prior to the start of study drug administration): (1) at least 3 joints with pain/tenderness and limitation of motion of the 74 joints assessed, (2) at least 5 inflamed, swollen joints of the 74 joints assessed, (3) ESR (Westergren method) ≥ 30 mm/hr or CRP ≥ 1.0 mg/dL.

set¹¹ on the last observation day was 94.7 % (18 of 19 subjects). The percentages of subjects showing 50% and 70% improvements in the JIA core set were 94.7 % (18 of 19 subjects) and 57.9 % (11 of 19 subjects), respectively (see the figure on the right).

Concerning the time course of CRP up to the last observation day in the FAS, a secondary endpoint, the CRP level was 2.63 ± 1.99 mg/dL (mean \pm SD) at baseline (before the administration of MRA), which

was reduced at 2 weeks post-dose and then changed slightly, but was 0.64 ± 1.50 mg/dL on the last observation day (CRP normalization rate [the proportion of subjects with a reduction of CRP to <0.5 mg/dL] was 84.2 % [16 of 19 subjects]). As to the time course of pain up to the last observation day, the number of joints with pain was 15.0 ± 10.9 joints at baseline and 1.5 ± 1.4 joints on the last observation day and the VAS pain score was 64.2 ± 27.5 at baseline and 30.6 ± 25.2 on the last observation day.

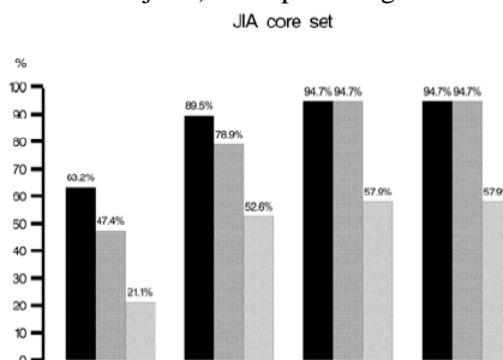


Figure. JIA core set response rates on the last observation day

Adverse events (including abnormal laboratory changes) occurred in 89.5 % (17 of 19 subjects, 38 events). Although serious adverse events were reported by 3 subjects (gastroenteritis, bacterial gastroenteritis, and sensory disturbance), a causal relationship to the study drug was denied for all cases and the outcome of sensory disturbance was reported as “recovering/resolving” and the outcomes of the other 2 cases were reported as “recovered/resolved.” No deaths occurred and there were no adverse events leading to treatment discontinuation. Adverse drug reactions were observed in 68.4% (13 of 19 subjects, 21 events) and the main events (excluding abnormal laboratory changes) were upper respiratory tract infection in 5 subjects (26.3 %), nasopharyngitis in 4 subjects (21.1 %), and diarrhoea in 2 subjects (10.5 %) etc., which were all mild in severity.

Abnormal laboratory changes were noted in 10.5 % (2 of 19 subjects, 2 events) (blood urine present and lymphocyte count decreased), which were both classified as adverse drug reactions, but were rated as mild in severity. Although the mean ALP tended to increase, deviating from

¹¹ 30% improvement in the JIA core set is defined as at least 30 % improvement from baseline in any three of the following six variables in the core set, with no more than one of the remaining variables worsening by more than 30 %; 50% and 70% improvements are also defined in the same manner. 1. Physician global assessment of disease activity (VAS), 2. Parent/legal guardian or patient global assessment of overall well-being (VAS), 3. Functional ability (Japanese version of CHAQ), 4. Number of active joints, 5. Number of joints with limited range of motion, 6. ESR.

the normal range, there were no patients with a change by two or more grades according to the NCI-CTC (National cancer institutes common toxicity criteria).

Infusion reactions occurred in 10.5 % (2 of 19 subjects, 2 events) (nausea [at the 1st dose] and dizziness [at the 3rd dose]) and the nausea was classified as an adverse drug reaction, but no similar events recurred thereafter. One subject was tested positive for anti-MRA antibodies (neutralizing antibody) on the last observation day.

Based on the above, the applicant explained that MRA is effective in pJIA patients and the safety profile of MRA is also tolerable.

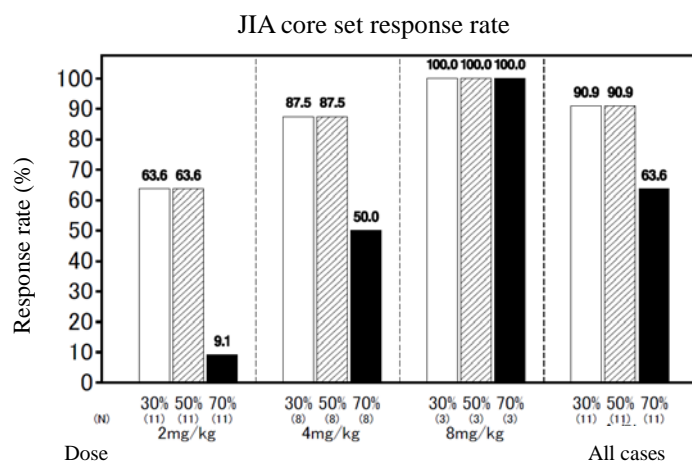
4.(iii).A.(8) Early phase II study in sJIA patients (Attached document 5.3.5.2-sJIA-1, MRA011JP [■■■ 20■■■ to ■■■ 20■■■])

An open-label study in Japanese sJIA patients aged at least 2 years old and less than 20 (under 16 years of age at onset) (target number of cases: 10) was conducted to evaluate the efficacy, safety, and pharmacokinetics of MRA. In the main evaluation period, MRA was initiated at 2 mg/kg every 2 weeks. The dose of MRA was to be increased to 4 mg/kg if CRP was ≥ 1.5 mg/dL after the 1st or 2nd dose and then further increased to 8 mg/kg if the effect of 4 mg/kg was considered inadequate based on the same criteria and the final dose of MRA was to be administered intravenously three times at 2-week intervals. In the continued treatment period, patients who completed the main evaluation period at 2 mg/kg were to receive MRA at doses up to 4 mg/kg and patients treated with an increased dose of 4 mg/kg or 8 mg/kg in the main evaluation period were to receive MRA at doses up to 8 mg/kg. The dosing interval was set at a minimum of 1 week. Since an interim evaluation by the Data and Safety Monitoring Board confirmed the safety of MRA at doses up to 8 mg/kg, the maximum dose was then changed to 8 mg/kg in all cases. The treatment period was 42-98 days in the main evaluation period and at least 1 year in the continued treatment period.

All of the 11 treated subjects were included in the safety analysis and in the FAS for efficacy. The final dose of MRA in the main evaluation period was 2 mg/kg in 3 subjects, 4 mg/kg in 5 subjects, and 8 mg/kg in 3 subjects, and in the continued treatment period, 10 out of the 11 subjects eventually received MRA 8 mg/kg at a minimum of one-week intervals.

The primary endpoint was the time course of CRP in the FAS. CRP declined after the 1st dose at all dose levels (2, 4, and 8 mg/kg), remained low throughout the study period, and was ≤ 0.1 mg/dL on the last observation day of the main evaluation period in all subjects. The CRP normalization rate (the proportion of subjects with a reduction of CRP to ≤ 0.2 mg/dL¹²) at each dose level at the last observation in the main evaluation period (calculated including subjects whose final dose was 4 or 8 mg/kg) was 27.3% during the

period when 2 mg/kg was administered, 62.5% during the period when 4 mg/kg was administered, and 100% during the period when 8 mg/kg was administered. Likewise, ESR declined after the 1st dose of MRA and was



13.7 mm/hr in the 2 mg/kg group, 3.4 mm/hr in the 4 mg/kg group, and 1.3

Figure. JIA core set response rates in the main evaluation period

mm/hr in the 8 mg/kg group on the last observation day of the main evaluation period. The ESR normalization rate (the proportion of subjects with a reduction of ESR to ≤ 10 mm/hr for men and ≤ 15 mm/hr for women) at each dose level at the last observation in the main evaluation period was 27.3% during the period when 2 mg/kg was administered, 75.0% during the period when 4 mg/kg was administered, and 100 % during the period when 8 mg/kg was administered.

Secondary endpoints, i.e. the percentages of subjects showing 30%, 50% and 70% improvements in JIA core set in the main evaluation period were 90.9%, 90.9% and 63.6%, respectively, when all subjects were included in the analysis. These figures were 63.6%, 63.6%, and 9.1%, respectively, during the period when 2 mg/kg was administered, 87.5%, 87.5%, and 50.0%, respectively, during the period when 4 mg/kg was administered, and were all 100.0% during the period when 8 mg/kg was administered (see the above figure).

Adverse events (including abnormal laboratory changes) occurred in all of the 11 subjects (a total of 214 events) during the main evaluation period and continued treatment period combined. Serious adverse events were observed in 7 subjects (10 events), which include gastroenteritis (3

¹² In this study, the upper limit of reference range of the institution (≤ 0.2 mg/dL) was used for determining the CRP normalization rate.

events), pneumonia, duodenal perforation, intussusception, inguinal hernia, erythema multiforme, rash, and joint dislocation (1 event each), among which, gastroenteritis (2 events), pneumonia, duodenal perforation, and erythema multiforme (1 event each) were classified as adverse drug reactions, but all of these events resolved or recovered. An adverse event leading to treatment discontinuation was duodenal perforation in 1 subject, which was “severe” in severity. There were no deaths.

Adverse drug reactions (including abnormal laboratory changes) occurred in all of the 11 subjects (162 events) and the main events (excluding abnormal laboratory changes) were gastroenteritis (90.9%, 10 subjects), nasopharyngitis (90.9%, 10 subjects), upper respiratory tract infection (63.6%, 7 subjects), abscess limb (54.5%, 6 subjects), eczema (45.5%, 5 subjects), bronchitis (36.4%, 4 subjects), and constipation (36.4 %, 4 subjects) etc. The main abnormal laboratory findings were ALT increased (54.5%, 6 subjects), β -N-acetyl-D-glucosaminidase increased (54.5%, 6 subjects), AST increased (36.4%, 4 subjects), blood cholesterol increased (36.4%, 4 subjects), and blood immunoglobulin G decreased (36.4%, 4 subjects) etc.

As an infusion reaction, only malaise occurred in one subject. There were no anti-MRA antibody-positive subjects.

Based on the above, the applicant explained that the tolerability of MRA 8 mg/kg given at 2-week intervals in sJIA patients has been confirmed and its efficacy has been suggested.

4.(iii).A.(9) Phase III study in sJIA patients (Attached document 5.3.5.1-sJIA-1, MRA316JP [■■■ 20■■■ to ■■■ 20■■■])

A study with an uncontrolled, open-label phase followed by a randomized, placebo-controlled, double-blind phase was conducted to evaluate the efficacy, safety, and pharmacokinetics of MRA. Eligible patients were defined as Japanese sJIA patients aged at least 2 years old and less than 20 (under 16 years of age at onset) who had been treated with corticosteroids (continued treatment for 3 months or longer at a dose of ≥ 0.2 mg/kg prednisolone equivalent) but who failed to respond adequately or in whom treatment could not be continued or the dose could not be increased due to adverse drug reactions (target number of cases: 45, 20 cases per group in the double-blind phase, allowing for dropouts during the open-label phase). Three intravenous doses of MRA 8 mg/kg were given at 2-week intervals in the open-label phase and patients who achieved CRP < 0.5 mg/dL and 30% improvement in the JIA core set on the last observation day of the open-label phase were to enter the double-blind phase (the transition period was 0 or 1 day) and receive six intravenous doses of MRA 8 mg/kg or placebo at 2 week-intervals. The

treatment period was 6 weeks in the open-label phase and 12 weeks in the double-blind phase.

All of the 56 treated subjects in the open-label phase were included in the safety analysis, the FAS for efficacy, and the PPS. Of the 50 subjects who completed the open-label phase, 44 subjects who met the entry criteria (placebo group, 23 subjects; MRA group, 21 subjects) entered the double-blind phase. In the double-blind phase, all subjects in the placebo group were included in the safety analysis, the FAS for efficacy, and the PPS, and all subjects in the MRA group were included in the safety analysis, 20 subjects excluding 1 subject in which the blindness could not be maintained¹³ were included in the FAS for efficacy, and 19 subjects excluding 1 subject with violations as to concomitant medications were included in the PPS.

The primary endpoint for the open-label phase, which was the percentage of subjects showing 30% improvement in the JIA core set on the last observation day, was 91.1% (51 of 56 subjects; 95% confidence interval, 80.4-97.0). The percentages of subjects showing 50% and 70% improvements in the JIA core set were 85.7% (48 of 56 subjects) and 67.9% (38 of 56 subjects), respectively. The CRP improvement rate on the last observation day (the proportion of patients with a reduction of CRP to <0.5 mg/dL) was 85.7% (48 of 56 subjects; 95% confidence interval, 73.8-93.6). As to the time courses of CRP and ESR up to the last observation day, i.e. secondary endpoints, the CRP and ESR levels declined at 2 weeks after the start of MRA administration and then remained low and were both significantly lower on the last observation day, compared to the baseline values ($p < 0.001$, paired t-test). Likewise, with respect to the time courses of the percentages of subjects showing 30%, 50%, and 70% improvements in the JIA core set, the JIA core set variables, pain (VAS), maximum body temperature, and the systemic feature score¹⁴ up to the last observation day, there were improvements on the whole.

The primary endpoint for the double-blind phase, which was the percentage of subjects in whom effects were maintained¹⁵, was 17.4% (4 of 23 subjects, 95% confidence interval, 5.0-38.8) in the placebo group and 80.0% (16 of 20 subjects, 95% confidence interval, 56.3-94.3) in the MRA group, showing a significant difference in favor of the MRA group ($p < 0.001$, χ^2 test [exact], see the figure below).

¹³ Due to human errors in the central laboratory, this subject received double-blind treatment while the subject's data on the blinded parameters during the double-blind phase (serum MRA concentration, IL-6, sIL-6R) were being disclosed to the clinical study site.

¹⁴ Systemic-onset JIA was assessed by the sum of the eight individual features (fever, rash, cervical lymphadenopathy, axillary lymphadenopathy, inguinal lymphadenopathy, hepatomegaly, splenomegaly, and serositis), which were scored as either absent (0 points) or present (1 point).

¹⁵ The percentage of subjects who completed the last observation without being withdrawn from the study due to meeting the withdrawal criteria or without meeting the rescue criteria during the double-blind phase (Subjects who had a CRP that increased to ≥ 1.5 mg/dL or did not maintain 30% improvement in the JIA core set during the double-blind phase were to receive rescue treatment and were withdrawn from the study after the last observation.)

Throughout the open-label and double-blind phases, adverse events (including abnormal laboratory changes) occurred in 98.2% (55 subjects) of the 56 subjects treated with MRA (273 events). Serious adverse events occurred in 2 subjects (anaphylactoid symptoms and gastrointestinal haemorrhage, one case each) during the open-label phase and the both events were classified as adverse drug reactions, but resolved or recovered following treatment discontinuation. Adverse events leading to treatment discontinuation were reported in 2 subjects (anaphylactoid symptoms and gastrointestinal haemorrhage) during the open-label phase and in 1 subject each in the placebo group and the MRA group (herpes zoster and ALT increased, respectively) during the double-blind phase. Adverse drug reactions were

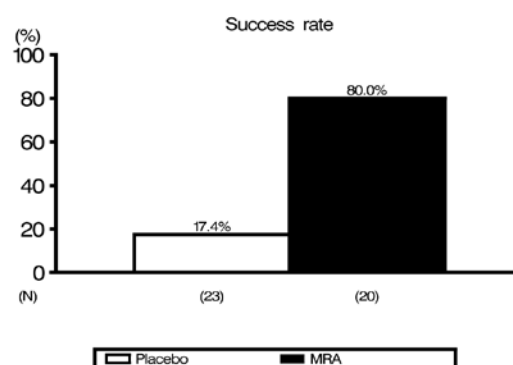


Figure. The percentage of subjects in whom effects were maintained in the double-blind phase

observed in 94.6% (53 subjects) of the 56 subjects treated with MRA (206 events), and the main events (excluding abnormal laboratory changes) were nasopharyngitis (26.8%, 15 subjects), upper respiratory tract infection (19.6%, 11 subjects), pharyngitis (12.5%, 7 subjects), gastroenteritis (10.7%, 6 subjects), and vomiting (10.7%, 6 subjects) and the main abnormal laboratory findings were ALT increased (23.2%, 13 subjects), AST increased (14.3%, 8 subjects), blood cholesterol increased (14.3%, 8 subjects), and lymphopenia (10.7%, 6 subjects), which were all mild or moderate in severity. During the double-blind phase, adverse drug reactions were reported in 19 subjects in the MRA group (73 events) and 23 subjects in the placebo group (89 events), and the main events (excluding abnormal laboratory changes) were nasopharyngitis (MRA group, 8 subjects; placebo group, 6 subjects), upper respiratory tract infection (MRA group, 3 subjects; placebo group, 7 subjects), pharyngitis (MRA group, 3 subjects; placebo group, 4 subjects), gastroenteritis (MRA group, 3 subjects; placebo group, 2 subjects), vomiting (MRA group, 3 subjects; placebo group, 1 subject), upper respiratory tract inflammation (MRA group, 3 subjects; placebo group, 2 subjects), pruritus (MRA group, 1 subject; placebo group, 4 subjects), diarrhoea (MRA group, 1 subject; placebo group, 3 subjects), and stomatitis (MRA group, 1 subject; placebo group, 3 subjects) and the main abnormal laboratory findings were ALT increased (MRA group, 5 subjects; placebo group, 6 subjects), AST increased (MRA group, 4 subjects; placebo group, 3 subjects), lymphocyte count decreased (MRA group, 2 subjects; placebo group, 4 subjects), blood cholesterol increased (MRA group, 2 subjects; placebo group, 3 subjects), blood immunoglobulin G decreased (MRA group, 1 subject; placebo group, 3 subjects), blood alkaline phosphatase increased (MRA group,

1 subject; placebo group, 4 subjects), blood lactate dehydrogenase increased (MRA group, 2 subjects; placebo group, 1 subject), and neutrophil count decreased (MRA group, 2 subjects; placebo group: 2 subjects).

During the open-label phase, infusion reactions occurred in 17.9% (10 subjects, 19 events) (chills in 5 subjects, pyrexia in 4 subjects, headache and vomiting in 3 subjects each, nausea in 2 subjects, anaphylactoid reaction and pruritus in 1 subject each). These infusion reactions occurred at the 1st infusion in 2 subjects (2 events), at the 2nd infusion in 6 subjects (14 events), and at the 3rd infusion in 3 subjects (3 events). During the double-blind phase (the 4th or subsequent infusions), infusion reactions occurred in 3 subjects in the MRA group (4 events) (headache, vomiting, pruritus, and blood pressure decreased).

Anti-MRA antibodies were detected in 4 of 56 subjects (IgE antibodies in all cases).

Based on the above, the applicant explained that although the incidence of adverse events with MRA in sJIA patients was high, there were no severe events and there should be no major problems with the tolerability of MRA at the proposed dosage regimen and the efficacy has also been confirmed.

4.(iii).A.(10) Long-term treatment study in RA patients—Extension study of the phase I/II study (Attached document 5.3.5.4-RA-1, MRA003JP [■ 20■ to ■ 20■ (ongoing)])

An open-label, uncontrolled study in patients enrolled into a phase I/II study for RA (MRA002JP) who wished to continue treatment (target number of cases: 15) is ongoing to evaluate the safety, efficacy, and pharmacokinetics of long-term treatment with MRA. At the time of filing the application, an interim report (data cutoff: ■ 20■) was submitted. Subjects were to receive MRA at doses up to 8 mg/kg every 2-4 weeks and adjustments in the dose and dosing interval were allowed according to clinical symptoms and changes in clinical laboratory values. The target duration of treatment was at least 1 year from the first dose in the previous study.

All of the subjects treated with the study drug in Study MRA002JP were enrolled into this study and all of the 15 enrolled subjects were included in the safety analysis, the FAS for efficacy, and the PPS. As of January 2005, 8 subjects were receiving MRA and 7 subjects were discontinued from treatment and the main reasons for withdrawal in this study were adverse events (3 subjects), subject request for withdrawal (1 subject), and lack of efficacy/exacerbation of symptoms (1 subject) etc.

The mean duration of treatment in the current and previous studies combined was 1307 days (as of January 2005 [data cutoff]). The percentage of ACR20 responders was 73.3% (11 of 15 subjects) at Week 12, 86.7% (13 of 15 subjects) at Week 24, 76.9% (10 of 13 subjects) at Week 48, 90.0% (9 of 10 subjects) at Week 108, 90.0% (9 of 10 subjects) at Week 156, 100.0% (9 of 9 subjects) at Week 204, 100.0% (8 of 8 subjects) at Week 240, and 100.0% (5 of 5 subjects) at Week 264.

During the study period including the previous study, adverse events (including abnormal laboratory changes) were reported in 100.0% (15 of 15 subjects, 325 events) as of January 2005 (data cutoff). Serious adverse events were observed in 7 subjects (16 events) and urinary tract infection/cellulitis/platelet count decreased, herpes zoster, rheumatoid arthritis, subcutaneous abscess, and angina pectoris/electrocardiogram T wave inversion, one case each, were classified as adverse drug reactions, but the outcomes of these events except for rheumatoid arthritis were reported as “recovered/resolved” or “recovering/resolving.” No deaths occurred. Adverse drug reactions (including abnormal laboratory changes) were observed in 100.0% (15 of 15 subjects) (178 events), and the main events (excluding abnormal laboratory changes) were nasopharyngitis (53.3%, 8 subjects), iron deficiency anaemia (20.0%, 3 subjects), pharyngolaryngeal pain (20.0%, 3 subjects), and abdominal pain upper (20.0%, 3 subjects) etc. and the main abnormal laboratory findings were blood cholesterol increased (80.0%, 12 subjects), low density lipoprotein increased (66.7%, 10 subjects), blood triglycerides increased (40.0%, 6 subjects), and blood lactate dehydrogenase increased (33.3%, 5 subjects) etc. Adverse events leading to treatment discontinuation were platelet count decreased, femoral neck fracture, and angina pectoris/electrocardiogram T wave inversion, one case each.

Infusion reactions were reported in 46.7% (7 of 15 subjects, 7 events), of which, the events in 3 subjects (pyrexia in 2 subjects, urticaria in 1 subject) were classified as adverse drug reactions.

The development of anti-MRA antibodies was not detected.

Based on the above, the applicant explained that the safety and efficacy of long-term treatment with MRA in RA patients have been suggested.

4.(iii).A.(11) Long-term treatment study in RA patients—Extension study of the late phase II study (Attached document 5.3.5.4-RA-2, MRA010JP [■ 20■ to ■ 20■ (ongoing)])

An open-label, uncontrolled study in patients enrolled into the late phase II study for RA (MRA009JP) who received at least two doses of the study drug and wished to continue treatment (target number of cases: not more than the number of patients enrolled into Study MRA009JP) is ongoing to evaluate the safety and efficacy of long-term treatment with MRA. At the time of filing the application, an interim report (data cutoff: ■ 20■) was submitted. Subjects were to receive three doses of MRA 8 mg/kg at 4-week intervals and then receive MRA at doses up to 8 mg/kg every 2-4 weeks and adjustments in the dose/the dosing interval were allowed according to clinical symptoms and changes in clinical laboratory values. The target duration of treatment was at least 1 year from the first dose in the previous study.

Of the 163 subjects treated with the study drug in Study MRA009JP, 144 subjects were enrolled into this study and 143 subjects received MRA. All of the 153 subjects who received at least one dose of MRA in Study MRA009JP and this study were included in the safety analysis, 151 subjects excluding 2 subjects with violations as to the inclusion/exclusion criteria were included in the FAS for efficacy, and 143 subjects excluding 5 prematurely discontinued subjects and 3 subjects with violations as to concomitant medications were included in the PPS. As of April 2005, 105 subjects were receiving MRA and 38 subjects were discontinued from treatment and the main reasons for withdrawal in this study were adverse events (28 subjects), subject request for withdrawal (6 subjects), and the development of anti-MRA antibodies (1 subject) etc.

The mean duration of treatment in the current and previous studies combined was 989 days (as of ■ 20■ [data cutoff]). The percentage of ACR20 responders was 54.1% (79 of 146 subjects) at Week 12, 66.4% (87 of 131 subjects) at Week 24, 79.3% (96 of 121 subjects) at Week 48, 78.8% (82 of 104 subjects) at Week 108, and 85.0% (85 of 100 subjects) at Week 144.

During the study period including the previous study, adverse events (including abnormal laboratory changes) were reported in 99.3% (152 of 153 subjects, 2098 events) as of ■ 20■ (data cutoff). Serious adverse events were reported in 39.9% (61 of 153 subjects, 138 events), of which, those classified as adverse drug reactions were reported in 15.0% (23 of 153 subjects, 61 events) (pneumonia [7 events], herpes zoster [5 events], etc.), but the outcomes of these events were reported as “recovered/resolved” or “recovering/resolving,” except for EB virus reactivation-related event, spinal osteoarthritis, tendon rupture, finger deformity, and brain stem infarction. One subject with EB virus reactivation died in the previous study (MRA009JP).

Adverse drug reactions (including abnormal laboratory changes) were reported in 98.0% (150 of 153 subjects, 1320 events), and the main events (excluding abnormal laboratory changes) were nasopharyngitis (48.4%, 74 subjects), tinea infection (17.6%, 27 subjects), rash (13.1%, 20 subjects), headache (12.4%, 19 subjects), pruritus (11.1%, 17 subjects), and stomatitis (10.5%, 16 subjects) etc. and the main abnormal laboratory findings were blood cholesterol increased (51.0%, 78 subjects), blood triglycerides increased (27.5%, 42 subjects), white blood cell count decreased (20.3%, 31 subjects), ALT increased (19.0%, 29 subjects), high density lipoprotein increased (16.3%, 25 subjects), γ -GTP increased (15.0%, 23 subjects), blood lactate dehydrogenase increased (14.4%, 22 subjects), and AST increased (13.1%, 20 subjects) etc. A total of 30 subjects were discontinued from treatment due to the occurrence of adverse events in the current or previous study.

Infusion reactions occurred in 23.5% (36 of 153 subjects, 57 events). Of which, those classified as adverse drug reactions were reported in 17.0% (26 of 153 subjects, 41 events), and the main events were headache (4 subjects), cough (4 subjects), and dizziness (3 subjects) etc.

Anti-MRA antibodies were detected in 5 subjects. Of these 5 subjects, 3 subjects were discontinued from treatment due to the development of anti-MRA antibodies in the current or previous study and the other 2 subjects were also discontinued from treatment due to patient request and anaphylactoid symptoms. The antibodies were all IgE antibodies and no neutralizing antibodies were detected.

Based on the above, the applicant explained that the efficacy and maintenance of effects of long-term treatment with MRA in RA patients have been confirmed and the safety is also considered acceptable.

4.(iii).A.(12) Safety information from extension studies etc. in RA/pJIA patients

4.(iii).A.(12).1) Safety information from Japanese extension studies (data cutoff: August 2007)

In addition to the above-mentioned extension studies (Study MRA003JP and Study MRA010JP), Study MRA222JP (the extension study of Study MRA220JP or MRA221JP), Study MRA214JP (the extension study of Study MRA012JP), and Study MRA215JP (the extension study of Study MRA213JP) for RA patients, and Study MRA319JP (the extension study of study MRA318JP) for pJIA patients were ongoing in Japan as extension studies at the time of filing the application, and the combined safety information from the study data at the time of filing the application and interim reports on the extension studies (data cutoff: August 2007) was submitted. In all of these

ongoing extension studies, subjects were to receive MRA 8 mg/kg every 4 weeks, as a rule.

The safety analysis population included 601 RA patients treated with MRA and 19 pJIA patients treated with MRA and the mean duration of treatment was 1149 days in RA patients and 861 days in pJIA patients. Treatment was discontinued in 175 RA patients and 4 pJIA patients. The main reasons for withdrawal in RA patients were the occurrence of adverse events (99 subjects), the doctor's judgment that it is difficult to continue treatment (24 subjects), subject request for withdrawal (17 subjects), and the development of anti-MRA antibodies (11 subjects) etc. and the main reasons for withdrawal in pJIA patients were lack of efficacy/exacerbation of symptoms (2 subjects) etc.

Adverse events (including abnormal laboratory changes) occurred in 99.0% (595 of 601 subjects, 6679 events) in RA patients and 100.0% (19 of 19 subjects, 125 events) in pJIA patients. Serious adverse events were observed in 39.1% (235 of 601 subjects) in RA patients and 21.1% (4 of 19 subjects) in pJIA patients and those classified as adverse drug reactions were reported in 19.0% (114 of 601 subjects) and 10.5% (2 of 19 subjects), respectively. The common serious adverse drug reactions in RA patients were pneumonia (22 subjects), herpes zoster (12 subjects), cellulitis (11 subjects), pyelonephritis (4 subjects), gastroenteritis, pleurisy, bacterial pneumonia, hepatic function abnormal, and platelet count decreased (3 subjects each) and the common serious adverse drug reactions in pJIA patients were pneumonia (1 subject) and myasthenia gravis (1 subject). Deaths occurred in 1 subject with EB virus reactivation (Study MRA009JP), 1 subject with gastric cancer (Study MRA214JP), and 1 subject with pulmonary fibrosis/bronchopulmonary aspergillosis (Study MRA214JP), and the EB virus reactivation, the gastric cancer, and the pulmonary fibrosis were classified as adverse drug reactions.

Adverse drug reactions (including abnormal laboratory changes) occurred in 97.3% (585 of 601 subjects, 4254 events) in RA patients and 97.7% (18 of 19 subjects, 85 events) in pJIA patients. The main events in RA patients (excluding abnormal laboratory changes) were nasopharyngitis (52.4%, 315 subjects), upper respiratory tract inflammation (11.0%, 66 subjects), stomatitis (9.3%, 56 subjects), rash (9.3%, 56 subjects), headache (8.3%, 50 subjects), pharyngitis (8.2%, 49 subjects), eczema (7.7%, 46 subjects), pruritus (7.5%, 45 subjects), cystitis (7.2%, 43 subjects), pneumonia (6.8%, 41 subjects), and hypertension (6.7%, 40 subjects) and the main abnormal laboratory findings were blood cholesterol increased (45.1%, 271 subjects), low density lipoprotein increased (24.3%, 146 subjects), blood triglycerides increased (19.8%, 119 subjects), ALT increased (14.5%, 87 subjects), white blood cell count decreased (10.3%, 62 subjects), and AST increased (10.3%, 62 subjects) etc. The main events observed in pJIA

patients (including abnormal laboratory changes) were nasopharyngitis (73.7%, 14 subjects), upper respiratory tract infection (31.6%, 6 subjects), pharyngitis (26.3%, 5 subjects), upper respiratory tract inflammation (21.1%, 4 subjects), eczema (21.1%, 4 subjects), and stomatitis (15.8%, 3 subjects) etc.

Adverse events leading to treatment discontinuation were reported in 16.5% (99 of 601 subjects, 138 events) in RA patients and the main events were pneumonia (13 subjects) and cellulitis (4 subjects) etc. One pJIA patient was discontinued from treatment due to myasthenia gravis.

Infusion reactions were observed in 14.8% (89 of 601 subjects, 126 events) in RA patients and 10.5% (2 of 19 subjects, 2 events) in pJIA patients. Of which, those classified as adverse drug reactions were reported in 11.3% (68 of 601 subjects, 92 events) in RA patients and the main events were headache (13 subjects), blood pressure increased (12 subjects), pruritus (9 subjects), pyrexia (7 subjects), dizziness, blood pressure decreased, and malaise (5 subjects each), hypertension, cough, and rash (4 subjects each) etc. In pJIA patients, 1 case of nausea was classified as an adverse drug reaction.

4.(iii).A.(12).2) Safety information from foreign clinical studies (reference data)

As foreign clinical studies in RA patients, Study LRO300 (a phase I study) and Study LRO301 (a phase II, dose-ranging study) were completed at the time of filing the application and the safety information from these studies (the pooled data from the two studies) was submitted. In Study LRO300, a single dose of MRA (up to 10 mg/kg) was administered. In Study LRO301, MRA 2, 4, or 8 mg/kg alone or in combination with MTX was administered every 4 weeks.

The safety analysis population included 344 RA patients treated with MRA (Study LRO300, 34 subjects; Study LRO301, 310 subjects) and the mean duration of treatment was 98 days (Study LRO300, 29 days; Study LRO301, 106 days). Sixty-five patients were discontinued from treatment and the main reasons for withdrawal were the occurrence of adverse events (32 subjects), the doctor's judgment that it is difficult to continue treatment (19 subjects), and lack of efficacy/exacerbation of symptoms (11 subjects) etc.

Adverse events (including abnormal laboratory changes) were reported in 57.0% (196 of 344 subjects, 509 events), and serious adverse events were observed in 8.4% (29 of 344 subjects) and those classified as adverse drug reactions were reported in 4.1% (14 of 344 subjects). The common serious adverse drug reactions were sepsis (3 subjects), anaphylactic reaction, anaphylactic shock, and rheumatoid arthritis (2 subjects each) etc. Two deaths occurred

(myocardial ischaemia, lung neoplasm malignant) and a causal relationship to the study drug was denied for both cases.

Adverse drug reactions (including abnormal laboratory changes) were observed in 26.7% (92 of 344 subjects, 160 events). The main events (excluding abnormal laboratory changes) were nausea (1.5%, 5 of 344 subjects) and diarrhoea (1.2%, 4 of 344 subjects) etc.

Adverse events leading to treatment discontinuation occurred in 8.4% (29 of 344 subjects, 31 events) and the main events were rheumatoid arthritis (1.7%, 6 of 344 subjects), abnormal liver function tests (0.9%, 3 of 344 subjects), sepsis (0.6%, 2 of 344 subjects), and rash (0.6%, 2 of 344 subjects) etc.

Infusion reactions were reported in 17.2% (59 of 344 subjects, 76 events) and those classified as adverse drug reactions were observed in 7.6% (26 of 344 subjects, 31 events) and the main events were rash (2.3%, 8 of 344 subjects) etc.

4.(iii).A.(13) Safety information from an extension study etc. in sJIA patients

4.(iii).A.(13).1 Safety information from a Japanese extension study (data cutoff: August 2007)

An open-label, uncontrolled, extension study (Study MRA317JP) in sJIA patients enrolled into Study MRA011JP or Study MRA316JP who wished to continue treatment (target number of cases: 55) is ongoing to evaluate the safety, efficacy, and pharmacokinetics of long-term treatment with MRA. In addition, Study MRA324JP is ongoing as a long-term treatment study. The combined safety information from the Study MRA011JP and Study MRA316JP data and interim reports on these studies (data cutoff: August 2007) was submitted. In the extension study, MRA 8 mg/kg was to be administered every 2 weeks.

The safety analysis population included 128 sJIA patients treated with MRA and the mean duration of treatment was 668 days. Fourteen patients were discontinued from treatment and the main reasons for withdrawal were the occurrence of adverse events (8 subjects) and the development of anti-MRA antibodies (5 subjects) etc.

Adverse events (including abnormal laboratory changes) were reported in 93.8% (120 of 128 subjects, 1235 events). Serious adverse events were observed in 35.9% (46 of 128 subjects) and those classified as adverse drug reactions were observed in 25.8% (33 of 128 subjects) and the main events were gastroenteritis (6 subjects), pneumonia (5 subjects), ALT increased (3

subjects), and AST increased (3 subjects) etc.

Deaths occurred in 1 subject with haematophagic histiocytosis and 1 subject with cardiac amyloidosis in Study MRA324JP, and the haematophagic histiocytosis was classified as an adverse drug reaction.

Adverse drug reactions (including abnormal laboratory changes) were reported in 89.8% (115 of 128 subjects, 952 events), and the main events (excluding abnormal laboratory changes) were nasopharyngitis (50.8%, 65 subjects), upper respiratory tract infection (33.6%, 43 subjects), gastroenteritis (32.0%, 41 subjects), pharyngitis (25.0%, 32 subjects), and upper respiratory tract inflammation (21.1%, 27 subjects) etc. and the main abnormal laboratory findings were ALT increased (21.1%, 27 subjects), AST increased (15.6%, 20 subjects), lymphocyte count decreased (14.8%, 19 subjects), blood lactate dehydrogenase increased (13.3%, 17 subjects), and blood cholesterol increased (13.3%, 17 subjects) etc.

Adverse events leading to treatment discontinuation occurred in 7.8% (10 of 128 subjects, 10 events) (anaphylactoid reaction and infusion-related reaction [2 subjects each], herpes zoster, duodenal perforation, gastrointestinal haemorrhage, haematophagic histiocytosis, cardiac amyloidosis, and ALT increased [1 subject each]).¹⁶

Infusion reactions occurred in 17.2% (22 of 128 subjects, 40 events) and those classified as adverse drug reactions were observed in 17.2% (22 subjects, 39 events), and the main events were headache, pyrexia, chills, and vomiting (5 subjects each) etc.

4.(iii).A.(13).2) Safety information from a foreign clinical study (reference data)

As a foreign clinical study in sJIA patients, Study LRO320 (a phase II, single dose study) was completed at the time of filing the application and the safety information from this study was submitted. In this study, a single dose of MRA 2, 4, or 8 mg/kg was administered.

The safety analysis population included 18 sJIA patients treated with MRA and the mean duration of treatment was 15 days. No patients were discontinued from treatment.

Adverse events (including abnormal laboratory changes) were reported in 83.3% (15 of 18 subjects, 60 events), serious adverse events were observed in 22.2% (4 of 18 subjects), and the events classified as adverse drug reactions were observed in 5.6 % (1 of 18 subjects [2 events]),

¹⁶ Including two subjects who were discontinued from treatment due to adverse events in Study MRA316, but were enrolled into Study MRA317 and have been continuing treatment (herpes zoster, ALT increased).

herpes simplex and arthritis).

Adverse drug reactions (including abnormal laboratory changes) were observed in 16.7% (3 of 18 subjects, 8 events). The main events were AST increased (11.1%, 2 of 18 subjects), ALT increased (11.1%, 2 of 18 subjects), LDH increased (11.1%, 2 of 18 subjects), herpes simplex (5.6%, 1 subject), and arthritis (5.6%, 1 subject) etc. There were no adverse events leading to treatment discontinuation or infusion reactions.

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

4.(iii).B.(1) Efficacy and indications etc.

4.(iii).B.(1).1 Rheumatoid arthritis (RA)

a. Clinical positioning etc. of MRA

i) Choice between MRA and TNF inhibitors (infliximab and etanercept)

PMDA asked the applicant to explain their view on the choice between MRA and TNF inhibitors in the treatment of RA.

The applicant explained as follows:

Since there are no studies directly comparing the effects of MRA with those of TNF inhibitors, it is difficult to clearly define the positioning of MRA. However, based on the comparison of the results from Japanese dose-finding studies of infliximab, etanercept, and MRA (the table below) and the comparison of the results from foreign phase III studies of infliximab and etanercept with the results from a Japanese phase III study of MRA (the table below), it is considered that the efficacy of MRA is not inferior to those of TNF inhibitors. Regarding safety, as with TNF inhibitors, MRA also requires a special attention to the occurrence of infections, but an increased incidence of specific infections etc. has not been reported to date and there should be no particular safety concerns about MRA compared to TNF inhibitors, though it should be taken into consideration that MRA has been used in a limited number of patients, compared to infliximab and etanercept. Therefore, MRA can be positioned as being at least equivalent to currently available TNF inhibitors. As with TNF inhibitors, MRA should be used in patients who have had an inadequate response to existing therapies and in light of the inclusion criteria employed in clinical trials, the existing therapies should be defined as “one or more anti-rheumatic drugs.”

Table. Comparison of the results from Japanese dose-finding studies of MRA and commercially available TNF inhibitors

	MRA (Tocilizumab) Study MRA009JP (3 months)			Etanercept Study 202-JA (3 months)			Infliximab Study TA-650-P3-01 (14 weeks)		
	Placebo	4 mg/kg	8 mg/kg	Placebo	10 mg	25 mg	Placebo	3 mg/kg	10 mg/kg
ACR20	11.3% (6/53)	57.4% (31/54)	78.2% (43/55)	6.3% (3/48)	64.0% (32/50)	65.3% (32/49)	23.4% (11/47)	61.2% (30/49)	52.9% (27/51)
ACR50	1.9% (1/53)	25.9% (14/54)	40.0% (22/55)	0.0% (0/48)	32.0% (16/50)	26.5% (13/49)	8.5% (4/47)	30.6% (15/49)	35.3% (18/51)
ACR70	0.0% (0/53)	20.4% (11/54)	16.4% (9/55)	0.0% (0/48)	12.0% (6/50)	10.2% (5/49)	Unknown	Unknown	Unknown

(n)

Table. Comparison of the results from a Japanese phase III study of MRA with the results from foreign phase III studies of commercially available TNF inhibitors (1 year of treatment)

	MRA 8 mg/kg Study MRA012JP	Etanercept 25 mg Study ERA	Infliximab 3 mg/kg Study ATTRACT	Infliximab 10 mg/kg Study ATTRACT
ACR20	77.7% (122/157)	69% (142/207)	41.9% (36/86)	58.6% (51/87)
ACR50	64.3% (101/157)	48% (99/207)	-	-
ACR70	43.3% (68/157)	24% (49/207)	-	-

(n)

PMDA asked the applicant to explain the appropriateness of combination therapy of MRA and a TNF inhibitor and the considerations in switching from a TNF inhibitor to MRA or from MRA to a TNF inhibitor, from the safety standpoint.

The applicant explained as follows:

With respect to combination therapy of MRA and a TNF inhibitor, there have been no clinical studies or clinical experience and its efficacy and safety have not been established. Also in basic research etc., there have been no data suggesting the synergistic effect of MRA and a TNF inhibitor. Judging from the results from clinical trials, MRA even as a monotherapy is expected to exhibit good efficacy. Therefore, we think that combination therapy will produce little benefits. As to switching between a TNF inhibitor and MRA, since the co-existence of MRA and a TNF inhibitor in blood may amplify the risk of infections, the treatment should be switched to MRA or a TNF inhibitor after the drug is eliminated from blood. Taking into account that drug elimination from blood takes around 5-7 times the half-life of a compound (Nadai, Masayuki. *Japanese Journal of Pediatric Nephrology*. 2000;19:111-23), when switching from infliximab (mean blood half-life: about 175 hours) or etanercept (mean blood half-life: about 86 hours) to MRA, it is desirable that MRA should be initiated at ≥ 8 weeks or ≥ 4 weeks after the last dose of infliximab or etanercept, respectively and when switching from MRA to a

TNF inhibitor, a TNF inhibitor should be initiated at ≥ 8 weeks after the last dose of MRA (maximum blood half-life: about 203 hours). Furthermore, in view of the possibility that a TNF inhibitor may reactivate latent *Mycobacterium tuberculosis* localized to granulomas by inhibiting granulation tissue formation by TNF- α [see “4.(iii).B.(3) Safety”], patients receiving a TNF inhibitor while taking antituberculous drugs based on the results of history taking about tuberculosis, chest X-ray, and tuberculin test etc., should continue to take antituberculous drugs also after being switched to MRA.

PMDA considers as follows:

Although there is no major problem with positioning MRA as being almost equivalent to TNF inhibitors in the treatment of RA in clinical practice at present, it is recommended that the appropriate patient populations for MRA and TNF inhibitors and the choice between MRA and TNF inhibitors, etc. should be determined with cooperation of the relevant academic societies etc. after collecting sufficient information on the characteristics, safety, and efficacy of these drugs in future. In addition, as the mode of action is different between MRA and TNF inhibitors, it is envisaged that these drugs will be switched each other in medical practice. Therefore, it is also important to provide sufficient information on the safety and efficacy etc. of switching between these drugs to the medical practice so as to avoid the occurrence/increase etc. of adverse events caused by switching treatment in an inappropriate manner.

ii) Combination therapy with MTX

PMDA asked the applicant to explain the necessity of combination therapy of MRA and MTX, taking into account that combination therapy of MRA and MTX has been investigated only in a pharmacology study in Japan, though MTX is positioned as a standard treatment for RA.

The applicant explained as follows:

In a foreign LRO301 study evaluating the efficacy and safety of MRA 8 mg/kg monotherapy compared to MTX (10-25 mg/week)+MRA 8 mg/kg combination therapy, the percentages of ACR20 responders in the MRA monotherapy group and the MRA+MTX combination therapy group were 62.7% and 73.5%, respectively, the percentages of ACR50 responders were 41.2% and 53.1%, respectively, and the percentages of ACR70 responders were 15.7% and 36.7%, respectively, showing a trend towards enhanced efficacy with MRA+MTX combination therapy. On the other hand, regarding safety, although there were no significant differences in the incidence of adverse events between the MRA monotherapy group and the MRA+MTX combination therapy group, sepsis (2 subjects) and infective arthritis (1 subject) were observed only in the combination therapy group and there was a trend towards increased ALT and AST

levels with the combined use of MTX. Therefore, MRA monotherapy seems safer, but as the dose of MTX used in this study was higher than its approved dose in Japan (24 of 50 subjects [48%] in the MRA+MTX combination therapy group received MTX 15 or 17.5 mg/week), it is difficult to simply apply these results to Japan. Thus, we consider that there is no evidence for recommending MRA+MTX combination therapy in Japan under the current situation.

PMDA considers as follows:

The applicant's view on MRA+MTX combination therapy in Japan is justified, but it is also envisaged that combination therapy with MTX may be attempted, anticipating enhanced efficacy in medical practice. Therefore, it is necessary to investigate the actual use of combination therapy and the safety of combination therapy, etc. via post-marketing surveillance.

b. Appropriateness of efficacy assessment method for the inhibition of progression of structural joint damage

PMDA asked the applicant to provide a justification for conducting Study MRA012JP on the inhibition of progression of structural joint damage with an open-label design, without using a specific control drug such as MTX.

The applicant explained as follows:

According to the PFSB/ELD Notification No. 0217001 as of February 2006, "Guideline for Clinical Evaluation Methods of Antirheumatoid drugs," a control drug needs to be included for confirming the inhibition of progression of structural joint damage by an antirheumatic drug in a phase III study and current standard anti-rheumatic drugs in the world, such as MTX or salazosulfapyridine, are generally selected. However, this guideline was published after Study MRA0012JP was initiated and furthermore, although MTX and salazosulfapyridine have proven to slow bone/joint destruction in Europe and the US (John TS, et al. *Arthritis Rheum.* 2000;43 495-505), as the clinical doses of these drugs in Japan are about half the doses in Europe and the US, the effects of these drugs in slowing bone/joint destruction at the Japanese doses are unclear and it was considered inappropriate to select these drugs as a control. Among DMARDs that had proven to slow bone/joint destruction in Europe and the US at the time of initiating this study, only leflunomide was commercially available also in Japan, but a post-marketing survey of all treated patients was just started and it was too early to select it as a control drug. Under such circumstances, properly, a placebo-controlled study should be carried out. However, since an evaluation of the effects in slowing bone/joint destruction usually takes at least 1 year, it was difficult to administer placebo from an ethical point of view. Therefore, it was decided to conduct a superiority study of MRA to be compared to conventional DMARDs (excluding

biologics and leflunomide), which is more difficult than a placebo-controlled trial, without including a specific control drug. Moreover, since it was considered necessary to help minimize dropouts in order to obtain long-term radiographs as many as possible, it was decided to employ an open-label design so that conventional DMARDs can be used without any particular restrictions. Although the study design was not a double-blind trial, radiographic assessments of bone/joints for the primary endpoint were performed by two independent readers under a blinded condition and we consider that the objectivity in data assessment has been assured.

PMDA asked the applicant to discuss the cause for an extreme difference in the change in the total Sharp score (TSS) between the readers in some cases and explain its impact on the reliability of study results.

The applicant explained as follows:

Radiographs from 41 of 306 subjects with an inter-reader difference of >14 in the change in TSS were read again. As a result, radiographs from 24 subjects had an inter-reader difference of >14 again and based on the data from these 24 subjects, its cause was investigated. Generally, inter-reader differences in the change in the joint space narrowing score tended to be greater than inter-reader differences in the change in the erosion score and especially, the joint space narrowing score for the hands seemed to be the biggest factor producing inter-reader differences. Meanwhile, smallest detectable change (SDC) was defined based on the inter-reader variability in the change and subjects with a change exceeding SDC were determined to be those with a change exceeding the inter-reader variability, and the numbers of subjects with the changes in the erosion score, the joint space narrowing score, and the total Sharp score exceeding respective SDCs were compared between the MRA group and the control group, using χ^2 test and Cochran-Mantel-Haenszel test including RA duration as a covariate (van der Heijde D, et al. *Arthritis Rheum.* 2005;52:49-60). As a result, both tests demonstrated a significant difference in favor of the MRA group compared to the control group for all variables except for the joint space narrowing score and the Week 28's total Sharp score. Therefore, it is considered that inter-reader differences have little impact on the overall reliability of the results.

PMDA asked the applicant to discuss the clinical significance of differences in the erosion score, i.e. the primary endpoint for this study (MRA0012JP), between the MRA group and the conventional DMARDs group.

The applicant explained as follows:

The progression of bone erosion is a major cause for articular deformities, which was also used as an outcome measure in foreign clinical studies of etanercept and abatacept etc. and has been suggested to be a sensitive outcome measure. Thus, the erosion score has been chosen as the primary endpoint for this study. The results of comparison of the erosion score between the MRA group and the conventional DMARDs group in this study are presented in the following table. In terms of the ratio of the change per year before and after initiating the study, the degree of progression of bone erosion in the MRA group was 29.1% of that in the conventional DMARDs group. The frequency of subjects with progression in the erosion score at 52 weeks after the start of the study was calculated, defining the cutoff value as 0.5 (Desiree H, et al. *Arthritis Rheum.* 2002;47:215-8) and was 31.8% in the MRA group and 53.8% in the conventional DMARDs group (Namely, the frequency of subjects with no progression was 68.2% in the MRA group and 46.2% in the conventional DMARDs group), which can be interpreted as a $\geq 20\%$ increase in the proportion of subjects with no progression of bone erosion following treatment with MRA. Therefore, we think that the study results suggest that treatment with MRA inhibits the progression of bone/joint destruction and suppresses the progression of articular deformities in the long-term.

Table. Comparison of the erosion score between the MRA group and the conventional DMARDs group (Study MRA012JP)

	MRA group	Conventional DMARDs group
Mean disease duration (years)	2.2±1.4	2.4±1.3
Mean erosion score (before study)	13.8±24.6	13.9±21.7
Mean change in erosion score (1 year before study)	6.27	5.79
Mean change in erosion score (at the end of the study [1 year])	0.85±3.22	3.21±6.59
Ratio of the change per year	0.16	0.55

Mean ± SD

PMDA considers as follows:

It was not necessarily appropriate to conduct Study MRA012JP without a double-blind design, including DMARDs of any type at any dose etc. as a control group, in view of the stringency of comparison. However, it is understandable that ethical considerations for subjects were needed for conducting this study, and radiographic assessments were performed under a blinded condition, and the superiority of MRA over conventional DMARDs was tested. Taking account of these points etc., it is judged that this study has confirmed the efficacy of MRA in preventing structural damage of joints in RA patients. Also, since it is currently understood that the ultimate goals in the management of RA are not only to decrease joint pain but also to prevent joint damage (American College of Rheumatology Subcommittee on Rheumatoid Arthritis

Guidelines. *Arthritis Rheum.* 2002;46:328-346), including the inhibition of progression of structural joint damage in the RA indication for MRA is justified.

4.(iii).B.(1).2) pJIA

PMDA asked the applicant to clearly present the subtypes of juvenile idiopathic arthritis (JIA) for which MRA is to be indicated, based on the criteria of the International League of Associations for Rheumatology (ILAR) and provide a justification for including polyarticular-course JIA in the RA indication.

The applicant explained as follows:

JIA is the collective term for diseases with unknown cause associated with symptoms in joints that begin in children less than 16 years old and is classified into 7 categories: systemic arthritis, oligoarthritis, rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis, according to the ILAR classification (Petty RE. *J Rheumatol.* 1998;25 1991-1994). Of which, MRA will be indicated for JIA classified as oligoarthritis (extended oligoarthritis) or polyarthritis (RF-positive and RF-negative) that is active in multiple joints at the time of starting treatment (defined as “polyarticular-course JIA [pJIA]” in this application) and systemic JIA (sJIA). Since sJIA is accompanied by systemic symptoms, mostly remittent fever and is a very serious disease, it was decided to apply for an indication of sJIA separately from other types of JIA. On the other hand, pJIA is similar to RA in many aspects, e.g. clinical findings, autoantibodies such as RF, inflammatory cytokine profile, and HLA, and has been treated in the similar manner as RA in medical practice. Thus, we have judged that pJIA should be positioned as pediatric RA and included in the RA indication.

As Study MRA318JP for pJIA was conducted with an open-label design, PMDA asked the applicant to explain the basis for judging that the efficacy and safety of MRA in pJIA can be assured based on the results from this study.

The applicant explained as follows:

Concerning Study MRA318JP for pJIA, in view of the pathological similarity of pJIA and RA as well as ICH E11 “Clinical Investigation of Medicinal Products in the Pediatric Population” (PMSB/ELD Notification No. 1334 dated December 15, 2000), we considered that if the study confirms the safety of MRA in pJIA patients at a dosage regimen similar to that for RA and shows pharmacokinetic similarities between adult RA patients and pediatric pJIA patients, the efficacy data from RA patients can be extrapolated to pJIA. According to a survey conducted by

the Health Sciences Research Group in 2000, the incidence of JIA in Japan is 8.79 per 100 000 pediatric population. Furthermore, pJIA is treatable with existing therapies such as MTX in many cases. Therefore, assuming that there were not many eligible patients for a clinical trial, it was decided to conduct a small, open-label trial. The results from this study were compared to the results from Study MRA009JP for RA. As to pharmacokinetics, while the blood trough levels over time tended to be lower in pediatric pJIA patients than in adult RA patients, there were no major differences in the pharmacokinetic/pharmacodynamic relationship (serum MRA levels and CRP) between pJIA and RA [see “4.(ii).B *Outline of the review by PMDA*”]. Efficacy results were similar between pJIA and RA for comparable variables, i.e. CRP, ESR, number of joints with pain and swelling, VAS score and CHAQ score (the following table). Also regarding safety, there were no adverse events unique to pJIA patients. Therefore, we consider that the efficacy and safety of MRA in pJIA can be assured.

Table. Comparison of efficacy (change from baseline) between pJIA study (MRA318JP) and RA study (MRA009JP)

	Study MRA318JP	Study MRA009JP
n	19	55
Number of joint with pain	-13.5 ± 10.3	-11.5 ± 8.3
Number of Swollen joint	-8.8 ± 6.6	-8.9 ± 6.2
CRP (mg/dL)	-1.99 ± 1.85	-3.59 ± 5.33
ESR (mm/hr)	-31.2 ± 17.0	-53.9 ± 32.0
Patient VAS assessment (mm)	-31.0 ± 19.6	-32.6 ± 26.5
CHAQ/MHAQ	-0.43 ± 0.48	-0.38 ± 0.44

Mean ± SD

PMDA asked the applicant to explain their view on the positioning of existing therapies and MRA in the treatment of pJIA since the inclusion criteria of Study MRA318JP did not require patients to have an inadequate response to existing therapies etc.

The applicant explained as follows:

Although Study MRA318JP did not have an inclusion criterion that required patients to have an inadequate response to existing therapies etc., 19 enrolled patients were those with high disease activity¹⁷ and all of them had previously been treated with MTX and some of them had previously received a TNF inhibitor. The most common reason for discontinuation of these prior therapies was “ineffective” or “inadequate response” (MTX was discontinued for this reason in all cases). Therefore, patients enrolled into this study are considered as those refractory to existing anti-rheumatic drugs. Thus, we think that MRA should be used in pJIA patients who have had an inadequate response to one or more anti-rheumatic drugs, as with the case of RA.

¹⁷ Patients with at least 3 joints with pain/tenderness and limitation of motion, at least 5 inflamed, swollen joints, and inflammatory findings of ESR ≥30 mm/hr or CRP ≥1.0 mg/dL.

PMDA considers as follows:

There is no major problem with an understanding that RA and pJIA are similar diseases based on clinical symptoms, laboratory findings, and genetic background etc., and referring to the results from RA clinical studies etc., it is judged that the efficacy of MRA in pJIA has been confirmed. However, it is not appropriate to implicitly include pJIA in the RA indication and it is necessary to claim a pJIA indication separately and clearly specify the appropriate patient population and the dosage regimen for children, etc. so as to ensure the proper use of MRA in pJIA patients.

Among pJIA, extended oligoarthritis and RF-negative polyarthritis may be accompanied by extra-articular manifestations that do not usually occur with RA, e.g. uveitis, though the number is limited (Saurenmann RK, et al. *Arthritis Rheum.* 2007;56:647-657) and taking into account that uveitis can lead to blindness (Yancey C, et al. *Pediatrics.* 1993;92:295-6), it is necessary to determine the effects of MRA on pJIA patients with such extra-articular manifestations via post-marketing surveillance.

4.(iii).B.(1).3) sJIA

PMDA asked the applicant to explain their view on the clinical positioning of MRA in the treatment of sJIA, in view of existing therapies for sJIA and the clinical study populations, etc.

The applicant explained as follows:

In the treatment of sJIA, not only the symptoms of arthritis, but also severe inflammatory reactions such as remittent fever and serositis need to be controlled. NSAIDs are used in mild cases and corticosteroids are used in NSAID non-responders. In corticosteroid non-responders etc., immunosuppressants or DMARDs may be used concomitantly, but an adequate response can not be expected and these drugs are positioned as an adjunct to corticosteroids. A phase III study for sJIA (MRA316JP) included refractory sJIA patients who had previously been treated with corticosteroids for 3 months or longer at a dose of ≥ 0.2 mg/kg prednisolone equivalent but who failed to respond adequately or in whom treatment could not be continued or the dose could not be increased due to adverse drug reactions and the percentage of subjects showing 30% improvement in the JIA core set on the last observation day of the open-label phase during which three doses of MRA 8 mg/kg were administered at 2-week intervals was 91.1 % (51 of 56 subjects) and the CRP normalization rate (CRP < 0.5 mg/dL) was 85.7 % (48 of 56 subjects), demonstrating high improvement effects. The number of subjects who developed remittent fever $\geq 38^{\circ}\text{C}$, which is characteristic of sJIA, was 16 of 54 subjects (29.6 %) at baseline, which was

decreased to 3 of 49 subjects (6.1 %) at 2 weeks after three doses of MRA. Therefore, we think that MRA is positioned as a first-choice drug for sJIA patients who have responded inadequately to corticosteroids or in whom corticosteroids can not be continued or the dose of corticosteroids can not be increased due to adverse drug reactions.

PMDA asked the applicant to provide a justification for choosing the percentage of subjects showing 30% improvement in the JIA core set etc., instead of a measure of systemic symptoms, as the primary endpoint, in a phase III study for sJIA (MRA316JP).

The applicant explained as follows:

The JIA core set has officially been adopted by the PRINTO (Pediatric Rheumatology International Trials Organization) and the ACR etc. and is a standard method to assess the efficacy of drugs for JIA. It has been designed to enable a comprehensive judgment, focusing on arthritis, physical function, and overall well-being, so as to cover all subtypes. Therefore, we think that choosing the percentage of subjects showing 30% improvement in the JIA core set as the primary endpoint also for this study is justified. For assessment of systemic symptoms, maximum body temperature and systemic feature score¹⁸ etc. were included in the efficacy endpoints, but these systemic symptoms may not always be evident under the situation where a high dose of corticosteroids is used concomitantly and it is difficult from an ethical point of view to reduce the dose of corticosteroids or perform a wash-out until the symptoms become apparent. Therefore, these variables were not chosen as the primary endpoint.

PMDA asked the applicant to explain changes in the dose of corticosteroids in the continued treatment period of an early phase II study (MRA011JP) and the extension study (MRA317JP) of a phase III study (MRA316JP), where adjustments in the dose of corticosteroids were allowed.

The applicant explained as follows:

All of the 67 sJIA patients enrolled into these studies (as of March 2006) received concomitant corticosteroids and the mean dose (min-max) was 13.09 mg/day (0.6-36.9 mg/day) prednisolone equivalent at Week 12 of MRA treatment, 10.67 mg/day (0.6-27.7 mg/day) prednisolone equivalent at Weeks 12-24, 7.96 mg/day (0-21.4 mg/day) prednisolone equivalent at Weeks 24-36, and 5.90 mg/day (0-17.8 mg/day) prednisolone equivalent at Weeks 36-48, and the percentages of subjects with a $\geq 30\%$, $\geq 50\%$, $\geq 70\%$, and $\geq 90\%$ dose reduction from baseline

¹⁸ sJIA was assessed by the sum of the eight individual features (fever, rash, cervical lymphadenopathy, axillary lymphadenopathy, inguinal lymphadenopathy, hepatomegaly, splenomegaly, and clinical evidence of serositis), which were scored as either absent (0 points) or present (1 point).

at Week 48 (n=47) were 76.6 %, 57.4 %, 25.5 %, and 8.5 %, respectively, showing that a ≥ 50 % dose reduction was possible in more than half of the subjects, and some subjects could even be withdrawn from corticosteroids (7 subjects at Week 48). Therefore, although no criteria for changing the dose were specified and these are not the results of a rigorous investigation, we consider that the high usefulness of MRA has been suggested in terms of reducing the dose of corticosteroids as well.

PMDA considers as follows:

sJIA is characteristically accompanied by systemic symptoms and considering its seriousness, the improvement of systemic symptoms is especially important. Thus, for efficacy assessment of drugs for sJIA, it seems preferable to use a variable reflecting systemic symptoms more closely as the primary endpoint. However, under the current situation where a measure of systemic symptoms of sJIA has not been well established, it is understandable that the JIA core set response etc., which is a commonly used efficacy measure for JIA, were chosen as the primary endpoint. The phase III study has confirmed the efficacy of MRA based on this endpoint and has suggested a trend towards an improvement also in the time courses of maximum body temperature and systemic feature score, i.e. secondary endpoints. Moreover, the extension study etc. has indicated that MRA is also associated with a reduced dose of corticosteroids, which currently play a central role in the treatment of systemic (extra-articular) symptoms etc. of sJIA. Taking account of these points, it is judged that the efficacy of MRA in the treatment of sJIA, including systemic (extra-articular) symptoms, has been confirmed. However, as it is unclear how much MRA can contribute to the improvement of individual symptoms and whether MRA can improve the long-term prognosis, etc., it is recommended that the information relating to these points should also be collected and examined via post-marketing surveillance etc.

4.(iii).B.(1).4) Physicians' qualifications for using MRA for JIA patients

PMDA asked the applicant to explain their view on the necessity of limiting the use of MRA to pediatric rheumatologists and its feasibility (including the number of pediatric rheumatologists and obstacles due to an uneven geographical distribution of pediatric rheumatologists) for the following reasons:

While findings observed in sJIA patients are non-specific and diseases with similar pathology may not be differentiated from sJIA appropriately, a rapid diagnosis and treatment are needed due to its seriousness. Thus, a definitive diagnosis must be made by a specialist; similarly, a diagnosis of pJIA is based on the joint counts and requires the expertise of a specialist as well; and since persistent oligoarticular JIA according to the JIA classification criteria by the ILAR is

treatable with NSAIDs alone in many cases and its prognosis and treatment method are different from those of pJIA for which MRA is indicated, it is necessary to diagnose the subtype of JIA precisely prior to the use of MRA and active involvement of a specialist is important.

The applicant explained as follows:

There are currently 26 medical institutions with pediatric rheumatologists across Japan (Kanto, 14; Kinki, 5; Kyusyu, 4; Chubu, 2; Tohoku, 1), which are unevenly distributed across the regions. Thus, it is difficult to treat JIA patients with MRA at these medical institutions only and measures should be taken to allow other physicians to use MRA if they have been trained to diagnose and treat JIA and given advice on the use of MRA by physicians with clinical experience of using MRA, so that JIA patients scattered across Japan can be managed while ensuring specialized care. The training program for physicians will be determined in collaboration with the relevant academic societies etc. and a post-marketing survey will be conducted at specified medical institutions, specifying the physicians' qualifications. Furthermore, it will be stated in the "WARNING" section of the package insert that MRA should be used in RA or JIA patients under the supervision of a physician with adequate knowledge about MRA and experience in treatment of the disease.

PMDA considers as follows:

In light of the current situation, it is unavoidable to allow the use of MRA also by physicians who have been trained to diagnose JIA etc. by specialists, but in such case, the content of an appropriate special training for physicians to use MRA and assurance of its effectiveness will be important. With the cooperation of the relevant academic societies etc., a support system for physicians to use MRA, including a training program and cooperation with pediatric rheumatologists, needs to be put in place as soon as possible.

4.(iii).B.(1).5) The proposed indications

In view of the results from Japanese clinical studies for RA, pJIA, and sJIA and the applicant's responses to the questions etc., PMDA suggests that the indications should be amended as follows and existing therapies should separately be specified in the "Precautions for Indications" section.

[Indications]

- Treatment of the following diseases in patients who have had an inadequate response to existing therapies
Rheumatoid arthritis (including the inhibition of progression of structural joint damage),

polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

The appropriateness of the above will be determined, taking account of discussions with the expert advisors.

4.(iii).B.(2) Dosage and administration [see “4.(ii).B.(1) Pharmacokinetics of MRA and the dosage regimen”]

PMDA asked the applicant to explain a possible increase in the incidence or severity of adverse events due to elevations of MRA trough concentrations as MRA trough levels may well exceed 1 µg/mL, the assumed minimum effective blood MRA concentration, at the proposed dosage regimen, and to explain their view on the necessity of considering a dose reduction or a dosing interval extension based on CRP levels or MRA trough concentrations, in order to ensure safety.

The applicant explained as follows:

The mean and maximum MRA trough concentrations were 9.64 to 12.7 µg/mL and 28.6 to 33.3 µg/mL, respectively, at the sampling points after Week 12 in a phase III study for RA (MRA213JP), 11.1 to 15.1 µg/mL and 33.1 to 47.7 µg/mL, respectively, at the sampling points after Week 20 in a phase III study for RA (MRA012JP), 3.83 to 5.71 µg/mL and 11.8 to 21.5 µg/mL, respectively, at the sampling points up to Week 12 in a phase III study for pJIA (MRA318JP), and 41.9 to 54.7 µg/mL and 69.3 to 103 µg/mL, respectively, at the sampling points between Week 6 and Week 18 in the double-blind phase of a phase III study for sJIA (MRA316JP). In all diseases, there were subjects with serum MRA trough concentrations well exceeding 1 µg/mL. However, when the relationship between the serum MRA trough concentration and the number of adverse events in each disease was investigated, as shown in the following figures, there were no increases in adverse events associated with elevations of trough concentrations for all diseases. In terms of the severity of adverse events, there was no correlation between the serum MRA trough concentration at the last observation and the severity of adverse events occurring up to the last observation in the two phase III studies for RA (the table below). And, in the phase III studies for pJIA and sJIA, the reported events were all mild or moderate in severity and there were no severe events. Therefore, although a dosing interval extension etc. should be considered in individual patients in the event of an adverse event, it is unnecessary to adjust the dosage regimen based on CRP levels or MRA trough concentrations in all patients in order to ensure safety.

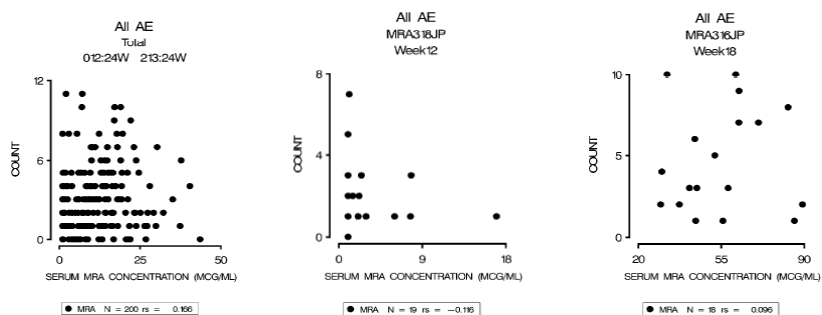


Figure. Serum MRA trough concentrations and the number of adverse events

Table. Serum trough concentrations and the occurrence of adverse events

	Below the quantification limit	1-10 µg/mL	10-20 µg/mL	≥20 µg/mL
n	30	67	75	46
Mild	81 (74.3)	252 (92.3)	327 (91.3)	200 (88.9)
Moderate	18 (16.5)	17 (6.2)	26 (7.3)	23 (10.2)
Severe	10 (9.2)	4 (1.5)	5 (1.4)	2 (0.9)
Total	109 (100.0)	273 (100.0)	358 (100.0)	225 (100.0)

n (%)

PMDA asked the applicant to explain the efficacy and safety in subjects treated at a reduced or extended dosing interval of MRA in clinical studies for RA, pJIA, and sJIA and their view on the necessity of adjusting the dosing interval (reduction or extension) according to the symptoms in each disease.

The applicant explained the efficacy and safety in subjects treated at a reduced or extended dosing interval of MRA in clinical studies for RA, pJIA, and sJIA as follows.

a. For RA, adjustments in the dosing interval were allowed according to clinical symptoms and changes in clinical laboratory values etc. in extension studies (MRA003JP, MRA010JP, MRA214JP, MRA215JP, MRA222JP). The reasons for adjusting the dosing interval could be investigated for 3 studies (MRA214JP, MRA215JP, MRA222JP). In these three studies, the periods during which at least three consecutive doses of MRA were administered at a reduced dosing interval for “efficacy” reasons were identified and the last ACR response rates before the reduction of the dosing interval were compared to the best ACR response rates at a reduced dosing interval. As a result, among the 21 relevant periods in 15 subjects, 8 periods in 7 subjects (38.1 %) had an increased ACR response rate at least once at a reduced dosing interval, 11 periods in 8 subjects (52.4 %) had no change, and 2 periods in 2 subjects (9.5 %) had worsening. Serum MRA trough concentrations were below the quantification limit in 9 of these 15 subjects, but reached ≥ 1 µg/mL at a reduced dosing interval in all of the 9 subjects. CRP levels were

positive before the reduction of the dosing interval in 9 of the 15 subjects, but normalized at a reduced dosing interval in all subjects. Regarding safety, none of the adverse events occurring during the periods with a reduced dosing interval had a particularly high incidence or high severity. In these studies, the reasons for extending the dosing interval were mostly “adverse events” and “the patient’s or medical institution’s convenience” and there were no specific adverse events associated with a dosing interval extension and there were also no rebound phenomena, e.g. an acute worsening of symptoms.

b. For pJIA, the dosing interval was allowed to be shortened to a minimum of 2 weeks or extended (no maximum interval was specified) in the extension study of Study MRA318JP. The dosing interval was shortened to ≤ 21 days for “efficacy” reasons in 9 subjects. In 6 out of these 9 subjects, serum MRA trough concentrations could not be maintained, which reached ≥ 1 $\mu\text{g/mL}$ at a reduced dosing interval in all cases and CRP also normalized. Of these 6 subjects, 3 subjects achieved a 70% JIA core set response at a reduced dosing interval, 2 subjects experienced no increased efficacy, and the remaining 1 subject, who was treated at a reduced dosing interval because CRP etc. did not normalize, maintained a 70% JIA core set response before and after the reduction of the dosing interval. On the other hand, in the other 3 of the 9 subjects, serum MRA trough concentrations were maintained. Of whom, 1 subject with a 50% JIA core set response achieved a 70% JIA core set response at a reduced dosing interval, and 2 subjects, who had achieved a 70% JIA core set response before the reduction of the dosing interval, had fewer joints with active arthritis at a reduced dosing interval. Regarding safety, there was no trend towards an increase in the incidence of adverse events at a reduced dosing interval. The dosing interval was extended to ≥ 35 days in 4 subjects, but the reasons for extending the dosing interval were all “the patient’s or medical institution’s convenience,” and there were no changes in the efficacy assessed by the JIA core set at an extended dosing interval, and there were no specific adverse events associated with a dosing interval extension.

c. For sJIA, the dosing interval was allowed to be shortened to a minimum of 1 week or extended (no maximum interval was specified) in the continued treatment period of Study MRA011JP and Study MRA317. In these studies, the dosing interval was reduced from 2 weeks to 1 week for consecutive doses for “efficacy” reasons in 6 subjects. In 4 of these 6 subjects, the trough concentrations immediately before the reduction of the dosing interval were low (below the detection limit or up to 8.4 $\mu\text{g/mL}$) and either CRP normalization or a 70% JIA core set response was not achieved, but CRP normalized and a 70% JIA core set response was achieved at a reduced dosing interval in all cases. The remaining 2 subjects had trough levels of 45.3 $\mu\text{g/mL}$ and 67.2 $\mu\text{g/mL}$, respectively, but were treated at a reduced dosing interval due to a rapid

increase in serum IL-6. One of them showed a 70% JIA core set response, then a 50 % JIA core set response and then achieved a 70% JIA core set response again at a reduced dosing interval. The other subject maintained a 70% JIA core set response before and after the reduction of the dosing interval. Regarding safety, none of the adverse events occurring during the periods with a reduced dosing interval had a particularly high incidence or high severity. There were 30 periods in 22 subjects during which at least three consecutive doses of MRA were administered at an extended dosing interval (at ≥ 3 -week interval) due to the sustained efficacy. In these subjects, a 70% JIA core set response and CRP normalization were maintained in almost all of these periods with an extended dosing interval. Also, in these studies and an open-label, clinical study (Study MRA324JP), the dosing interval was extended for 189 doses in 73 of the 91 subjects (80.2 %). The reasons for extending the dosing interval were “sustained efficacy” for 90 doses (47.6 %), “adverse events” for 41 doses (21.7 %), and “the patient’s or medical institution’s convenience” for 64 doses (33.9 %) (more than one reason for some doses). The mean extended dosing interval (range) was 3.06 weeks (2.5-10 weeks) and the extended dosing intervals were mostly up to 3 weeks. Of the 73 subjects treated at an extended dosing interval, 5 subjects (6.8 %) had confirmed flares (less than 30% JIA core set response) and the time to flares was 18 to 427 days from the start of extension. The serum MRA concentrations during flares were less than 1 $\mu\text{g/mL}$ in 2 subjects and around 20 $\mu\text{g/mL}$ in 3 subjects and the CRP levels were elevated in one subject, but unchanged in the other subjects.

Based on the above, the applicant explained as follows:

In all the diseases, if patients have responded inadequately to MRA at the recommended dosage regimen, increased efficacy can be expected at a reduced dosing interval, but the background factors for which a dosing interval reduction should be recommended have not been identified. Especially in RA and pJIA, there are patients who experience therapeutic effects even though their serum MRA trough concentrations or CRP normalization can not be maintained. Therefore, in order to avoid an unnecessary reduction of the dosing interval, it is important to closely observe the clinical symptoms etc. first during treatment with MRA. Then, only when the improvement of the disease condition is considered inadequate, a dosing interval reduction should be considered. We are considering to include the following statement in the package insert for each disease: If the improvement of symptoms is inadequate and IL-6 inhibition is considered inadequate based on CRP levels, the dosing interval may be shortened by 1 week. For sJIA, a dosing interval extension in patients with sustained improvement of the disease condition has also been attempted, which has suggested that a dosing interval extension can also be feasible under the condition where the disease activity is sufficiently controlled at a significantly reduced dose of corticosteroids. However, this has been attempted only in a limited

number of patients and a method that can be generalized has not been established. Therefore, if the dosing interval is extended, a substantial extension should be avoided in order to prevent flares and careful management is needed, e.g. the dosing interval should be extended gradually while closely monitoring the clinical symptoms and markers of inflammation.

PMDA considers as follows:

It is theoretically understandable that if patients have responded inadequately to MRA at the recommended dosage regimen, the efficacy can be enhanced by reducing the dosing interval, but the efficacy and safety of MRA at a reduced dosing interval have not fully been confirmed at present. Thus, for at least RA and pJIA, it is not appropriate to include a recommendation to reduce the dosing interval in the package insert and it is necessary to further investigate its efficacy, safety, and appropriate adjustment method etc. after collecting the information. On the other hand, concerning sJIA, similarly to RA and pJIA, there has been no adequate scientific evidence supporting a dosing interval reduction, but considering the seriousness of the disease and the urgency of treatment as well, the necessity of a relevant statement in the package insert should be determined carefully. Therefore, a decision will be made, taking account of discussions with the expert advisors. In addition, since the effects of the total exposure to MRA on the long-term safety are unknown at present, the exposure should be minimized wherever possible and it is recommended that the method for extending the dosing interval and whether or not MRA should be interrupted, in the case of sustained improvement of the disease condition following treatment with MRA, should also be further investigated in future.

4.(iii).B.(3) Safety¹⁹

4.(iii).B.(3).1) Common adverse events and serious adverse events etc.

a. Infections

i) Caution statements about infections as a whole

PMDA asked the applicant to sort out and present “infections and infestations” among adverse events reported in Japanese clinical studies and to explain whether adequate caution statements about infections are included in the package insert (draft), taking into account that the suppression of inflammatory markers by MRA may delay the detection of infections, leading to serious infections.

¹⁹ The safety of MRA was reviewed based mainly on the safety data (total 1110 cases) from Japanese clinical studies (the evaluation data), foreign clinical studies that were complete at the time of filing the application and submitted as the reference data (LRO300, LRO301, LRO301A, LRO320), and the interim reports on the extensions of these studies (data cutoff: August 2007). The information on serious adverse events collected from the overall MRA safety population (approximately 4600 cases, data cutoff: September 2007), including clinical studies for RA, pJIA, and sJIA that were ongoing at the time of submission or were initiated after submission, clinical studies for other diseases, and compassionate use data etc., was used as appropriate.

The applicant explained as follows:

As of ■■■ 20■■ (safety data cutoff), the incidences of “infections and infestations” among adverse events and adverse drug reactions in Japanese patients with RA, pJIA and sJIA included in the safety population are as shown in the following table. Infections occurred at a relatively high frequency following treatment with MRA. In three controlled studies for RA, the incidence of infections was higher in the MRA group than in the control group (the table below) and the severity was also higher. Serious infections such as pneumonia and sepsis, associated with MRA have been reported. Therefore, for MRA, infections are the adverse event that we should be most cautious about.

Table. Incidence of “infections and infestations” in the Japanese safety population

	RA	pJIA	sJIA
Adverse events	83.0% (499/601 subjects)	94.7% (18/19 subjects)	80.5% (103/128 subjects)
Adverse drug reactions	78.0% (469/601 subjects)	89.5% (17/19 subjects)	78.9% (101/128 subjects)
Serious adverse events	Pneumonia (including bacterial pneumonia), 25 subjects/27 events; herpes zoster, 12 subjects/12 events; cellulitis, 11 subjects/12 events, etc.	Pneumonia, 1 subject/1 event; myasthenia gravis, 1 subject/1 event	Gastroenteritis, 6 subjects/7 events; pneumonia, 5 subjects/8 events, etc.

Table. Incidence of “infections and infestations” in controlled clinical studies

	MRA group		Control group		
	4 mg/kg	8 mg/kg	Placebo	Conventional DMARDs	MTX
Study MRA009JP	22.2% (12/54 subjects)	23.6% (13/55 subjects)	16.7% (9/54 subjects)	–	–
Study MRA012JP	–	58.0% (91/157 subjects)	–	51.0% (74/145 subjects)	–
Study MRA213JP	–	39.3% (24/61 subjects)	–	–	25.0% (16/64 subjects)

The use of MRA inhibits acute phase reactions such as CRP production and also suppresses the symptoms associated with infections, which may delay the detection of infections, leading to serious infections. Thus, prior to the use of MRA, it is important to carefully ascertain that the patient has no infections and patients with infections must be treated before treatment with MRA is initiated. It is also important to instruct the patient to consult his/her doctor promptly if the patient develops symptoms suspected of infections. In order to ensure that these actions will be taken appropriately, the following statements will be included in the “WARNING” section of the package insert: Serious infections may occur following treatment with MRA; and the effects of MRA may delay the detection of infections, leading to serious infections, etc. “Patients with

serious infections” and “patients with infections or suspected infections” will be listed in the “CONTRAINDICATIONS” section and the “Careful Administration” section, respectively. Furthermore, the following statements will be included in the “Important Precautions” section: Prior to the use of MRA, it should be checked whether the patient has infections; and if the patient has an infection, the infection should be treated first, etc.

PMDA asked the applicant to explain their view on the necessity of excluding patients at high risk for infections from treatment with MRA, e.g. by applying the exclusion criteria with respect to immunocompromised patients for each clinical study (white blood cell count $<3500/\text{mm}^3$, neutrophil count $<1000/\text{mm}^3$, lymphocyte count $<500/\text{mm}^3$) also after the market launch, in addition to the above-mentioned caution statements.

The applicant explained as follows:

The exclusion criterion as to neutrophil count was set for sJIA clinical studies only, because a transient decrease in neutrophil count was noted in a Japanese clinical study for sJIA. The exclusion criterion as to white blood cell count was set for Japanese clinical studies for RA, pJIA, and sJIA since a transient decrease in neutrophils was observed in a phase I study. The exclusion criterion as to lymphocyte count was set for Japanese clinical studies for RA, pJIA, and sJIA since a patient who died of EB virus reactivation had a very low lymphocyte count of $304/\text{mm}^3$ immediately before the first dose.

Then, the applicant responded as follows:

In Japanese clinical studies, there were no subjects with a white blood cell count below the threshold or a neutrophil count below the threshold before the first dose and no safety data from relevant patients treated with MRA are available. However, as adverse events such as febrile neutropenia and myelosuppression have not been reported so far, although attention needs to be paid to changes in these laboratory parameters following treatment with MRA, we think at present that it is unnecessary to apply the exclusion criteria as to white blood cell count and neutrophil count, as a post-marketing safety measure. On the other hand, lymphocyte count was below the threshold in 16 out of the 601 RA patients and 2 out of the 128 sJIA patients, of whom 4 patients developed serious infections (EB virus infection, upper respiratory inflammation, herpes zoster, and pneumonia, one case each) and the risk of infections appears to be high in patients with a low lymphocyte count. Therefore, the following statement will be added in the “Important Precautions” section of the package insert: Treatment with MRA should not be initiated if decreased lymphocyte count (approximately $<500/\text{mm}^3$) is prolonged.

PMDA considers that these caution statements about infections (draft) are appropriate at present, but after closely examining the data from patients with infections collected via post-marketing surveillance etc., the necessity of a further caution statement should be considered in future.

ii) Tuberculosis

Since 3 cases of tuberculosis²⁰ (2 cases of pulmonary tuberculosis, 1 case of miliary tuberculosis) have been reported in Study MRA214JP for RA, PMDA asked the applicant to discuss the effects of the inhibition of the IL-6/IL-6 receptor interaction on TNF- α and then explain their view on the necessity of stipulating mandatory tuberculosis screening and prophylactic administration of antituberculous drugs etc. in the package insert for MRA, as with TNF inhibitors.

The applicant explained as follows:

The development of tuberculosis associated with TNF inhibitors is considered attributable to the reactivation of latent *Mycobacterium tuberculosis* localized to granulomas resulting from the inhibition of granulation tissue formation by TNF- α (Ehlers S, et al. *J Rheumatol.* 2005;32:35-39), whereas there are no reports suggesting the involvement of IL-6 in granuloma formation following *Mycobacterium tuberculosis* infection and there is also no report available that IL-6 directly affects the production of TNF- α . Of the 3 subjects who developed tuberculosis in Study MRA214JP, one subject was diagnosed with tuberculosis due to a positive result on the Gaffky's scale, but the details are unknown. The remaining two subjects may have had latent infections, since one of them had a strongly positive tuberculin reaction before the administration of MRA and the other presented with trabecular and nodular shadows, which are considered to be caused by inflammation, on CT before study participation. However, while tuberculosis associated with TNF inhibitors occurs most frequently in a relatively early phase of treatment (median: Week 12, Weeks 1-52 [Joseph K, et al. *N Engl J Med.* 2001;345:1098-1104]), the time to onset in these three subjects was 1.5 to 2.5 years from the start of treatment with MRA. Thus, it is inferred that the mechanism of the development of tuberculosis following treatment with MRA is very likely to be different from granuloma breakdown and release of *Mycobacterium tuberculosis*. Furthermore, of the 748 patients who participated in the Japanese clinical studies, 14 patients had a history of tuberculosis, but none of them developed recurrent tuberculosis, without receiving concomitant antituberculous drugs during the MRA treatment period. Taking account of these findings, we think that there is no evidence suggesting that MRA is associated with the risk of developing clinically apparent tuberculosis in latent infection cases. Based on the above, in order to manage infections as a whole, it is important to perform

²⁰ According to the data from the safety population (data cutoff: ■ 20 ■), one case of tuberculosis has been reported in a foreign clinical study (Study WA18695), in addition to these cases.

screening tests for infections, including chest X-ray, and check the patient backgrounds, e.g. suspected old pulmonary tuberculosis on chest X-ray film, a positive tuberculin reaction, and a history of tuberculosis etc., but we think at present that precautionary measures against tuberculosis and caution statements about tuberculosis, separately from other infections, are unnecessary.

PMDA considers as follows:

Although at present, there is no clear evidence suggesting that MRA is associated with the risk of developing active tuberculosis, as the effects of the inhibition of IL-6 signal transduction on the behaviour of TNF- α are unclear, the necessity of precautionary measures against tuberculosis, etc. will be determined, taking account of discussions with the expert advisors.

iii) EB virus infection

Taking into account that one subject died of EB virus infection in Study MRA009JP for RA, PMDA asked the applicant to explain their view on the necessity of advising caution about EB virus infection.

The applicant explained as follows:

This subject had a history of an increase in EB viral load, serum EB virus DNA was detected before the administration of MRA, and anti-EADR IgG titre, which is indicative of a marked reactivation of EB virus, was high, i.e. 640-fold higher than the reference value. Therefore, it is considered that this subject had chronic active EB virus infection (CAEBV) and the possibility that MRA was involved in the reactivation of EB virus can not be ruled out, but we consider that this is not the case suggesting that MRA is associated with the risk of developing EB virus infection. Also, taking into account that this subject had a very low lymphocyte count of 304/mm³, patients with a lymphocyte count <500/mm³ were excluded from subsequent clinical studies and since then, the appearance of serious latent infections has not been reported. Therefore, as mentioned earlier, a caution statement about decreased lymphocyte count will be included in the package insert, which can reduce the risk of viral infections or reactivation of latent virus etc. also after the market launch. Furthermore, as the symptoms of CAEBV, i.e. pyrexia, lymphadenopathy, and hepatosplenomegaly, are similar to rheumatic diseases including sJIA and Castleman's disease, careful differentiation is required prior to the use of MRA. However, as the "Important Precautions" pertaining to infections as a whole, it is stated in the package insert that the clinical symptoms of the primary disease should be carefully differentiated from infections prior to the start of treatment with MRA. Thus, we think at present that a special caution statement about EB virus infection and CAEBV etc. is unnecessary.

PMDA understands, to some extent, the applicant's view that tuberculosis and CAEBV etc. can also be managed by caution statements about infections as a whole, but considers that MRA should be administered carefully in patients with a history of infectious diseases that can be reactivated. Therefore, the necessity of a more aggressive measure will be determined, taking account of discussions with the expert advisors.

b. Antibody formation

PMDA asked the applicant to explain the association between the dose/the number of doses of MRA etc. and the development of anti-MRA antibodies and the effects of antibody development on the efficacy and safety of MRA.

The applicant explained as follows:

In Japanese and foreign RA, pJIA (administered once every 4 weeks) and sJIA (administered once every 2 weeks) patients included in the safety population, 57 of 1110 patients were positive for anti-MRA antibodies (neutralizing antibodies: 20 patients, IgE antibodies: 45 patients, both antibodies: 8 patients). (a) The incidence of antibody formation by dose level is as shown in the following table and the incidence was decreased in a dose-dependent manner for both neutralizing antibodies and IgE antibodies, (b) The number of patients who developed antibodies by the number of doses was 2 patients after the 1st dose, 2 patients after the 3rd dose, and 12 patients after the 4th dose for neutralizing antibodies, and 10 patients after the 1st dose, 15 patients after the 2nd dose, 9 patients after the 3rd dose, and 5 patients after the 4th dose for IgE antibodies, (c) Of the 56 patients with positive anti-MRA antibodies (neutralizing antibodies and IgE antibodies) (excluding 1 patient tested positive before the administration of MRA), 37 patients continuously had serum MRA trough concentrations below the quantification limit up to the development of antibodies. Based on these findings, it seems that anti-MRA antibodies tend to develop in an early phase of treatment at a low dose of MRA and the risk of antibody formation is high in patients with serum MRA concentrations below the quantification limit. Concerning the effects on the efficacy of MRA, theoretically, the development of neutralizing antibodies diminishes the therapeutic effects, but there have been no patients who experienced decreased efficacy after the development of antibodies and its effects are unknown. Concerning the effects on the safety of MRA, theoretically, IgE antibodies are related to anaphylaxis, but anaphylactic symptoms occurred in 7 out of the 45 patients with positive IgE antibodies and not all the positive patients developed anaphylaxis, and there have so far been no adverse events specific to positive antibody cases, except for anaphylaxis.

Table. Comparison of the incidence of anti-MRA antibody formation between the doses

	MRA 2 mg/kg	MRA 4 mg/kg	MRA 8 mg/kg
n	145	177	788
Neutralizing antibodies	11 (7.6)	3 (1.7)	6 (0.8)
IgE antibodies	11 (7.6)	10 (5.6)	23 (2.9)

n (%)

PMDA asked the applicant to explain the effects of concomitant MTX etc. on anti-MRA antibody formation.

The applicant explained as follows:

In a foreign study LRO301 for RA, the incidence of anti-MRA antibody formation was compared between the MRA monotherapy group and the MRA+MTX combination therapy group (MTX 10-25 mg/week). As shown in the following table, it was indicated that the incidence of antibody formation was lower in the MRA+MTX combination therapy group compared to the MRA monotherapy group. Meanwhile, taking into account that the incidence of anti-MRA antibody formation was decreased at a higher dose of MRA and the risk of antibody development in the MRA 8 mg/kg monotherapy group, i.e. the proposed clinical dose, was as low as that in the MRA+MTX combination therapy group, we think that there is no need to administer MRA in combination with MTX etc. in terms of reducing the risk of antibody formation.

Table. Incidence of anti-MRA antibody formation in Study LRO301

	MRA 2 mg/kg	MRA 4 mg/kg	MRA 8 mg/kg	MRA 2 mg/kg + MTX	MRA 4 mg/kg + MTX	MRA 8 mg/kg + MTX
n	53	54	52	52	49	50
Neutralizing antibodies	10 (18.9)	2 (3.7)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
IgE antibodies	9 (17.0)	7 (13.0)	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)

n (%)

PMDA considers as follows:

At present, it is difficult to draw a conclusion on the effects of antibody development and it is important to continue to investigate the risk factors for antibody formation and the effects of antibody development on the efficacy, safety, and pharmacokinetics etc. of MRA after collecting/closely examining the information and to provide the results of these investigations to the medical practice appropriately. Although it is difficult to perform antibody testing following the administration of MRA in all patients, it is also necessary to perform antibody testing at least

in the event of infusion reactions etc. wherever possible and further investigate its relationship with antibody development.

c. Infusion reactions and anaphylaxis

PMDA asked the applicant to sort out infusion reactions and anaphylaxis reported in Japanese and foreign clinical studies and explain, in particular, potential preventive measures against anaphylaxis and actions to be taken in the event of anaphylaxis.

The applicant explained as follows:

In Japanese and foreign RA/pJIA patients included in the safety population, infusion reactions occurred in 150 of 964 patients (15.6%) (including 91 of 620 Japanese patients [14.7%]), the incidence of infusion reactions by the number of doses was highest at the 1st infusion, i.e. 56 of 964 patients (5.8%) and up to 3.2% at subsequent infusions. In 146 Japanese and foreign sJIA patients included in the safety population, infusion reactions occurred in 30 of 146 patients (20.5%) (including 22 of 128 Japanese patients [17.2%]), the incidence of infusion reactions by the number of doses was highest at the 1st infusion, i.e. 12 of 146 patients (8.2%) and up to 6.3% at subsequent infusions. Anaphylaxis (including anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and hypersensitivity) occurred in 13 of the 1110 Japanese and foreign RA/pJIA and sJIA patients included in the safety population and a causal relationship to MRA could not be denied for 9 patients (7 RA patients, 2 sJIA patients) including 1 Japanese patient with RA and 2 Japanese patients with sJIA (However, patients with positive anti-MRA antibodies were required to be withdrawn from Japanese clinical studies, which may result in the fewer cases with anaphylaxis). Of the 9 patients with anaphylaxis for which a causal relationship could not be denied, 7 patients were tested positive for anti-MRA antibodies (IgE) at the onset of anaphylactic symptoms or at 4 weeks after the onset of anaphylactic symptoms, but 2 patients were tested negative. As to the time to onset, anaphylaxis occurred in an early phase of treatment (the 2nd to 5th infusions) in all cases and anaphylaxis developed at 20-30 minutes after the start of infusion and none of the patients developed anaphylaxis at ≥ 1 hour after the start of infusion. Of the 45 patients with positive IgE antibodies, 7 patients had anaphylactic symptoms.

With respect to preventive measures against anaphylaxis, although many of the patients with anaphylaxis were positive for IgE antibodies, anaphylaxis was not limited to positive antibody patients. Conversely, not all the patients with positive antibodies developed anaphylaxis. Thus, an infusion method assuming the occurrence of anaphylaxis and furthermore, appropriate actions at the onset of symptoms are important, rather than periodic antibody testing etc.

Therefore, the following caution statements will be included in the package insert: The product is contraindicated in patients with a history of hypersensitivity to any of the components of the product; adhere to the dosage and administration instructions, since if the serum MRA trough concentration is kept below the quantification limit, anti-MRA antibodies are likely to develop; the infusion should be initiated slowly while carefully monitoring the patient's condition; and if anaphylactic shock etc. develops, discontinue treatment with MRA and ensure that medication therapy such as epinephrine, corticosteroids, and antihistamines, and emergency measures can be used immediately.

PMDA accepted the above response.

d. Macrophage activation syndrome (MAS)

sJIA patients may develop macrophage activation syndrome (MAS), which is different in pathology from severe or worsened cases of sJIA and in an ongoing open-label clinical study for sJIA (MRA324JP), MAS occurred in 2 subjects as of September 2007 and one of them died. In view of this finding, PMDA asked the applicant to explain their view on the potential induction of MAS by MRA and whether or not MRA should be administered in patients with MAS.

The applicant explained as follows:

It is considered that a cytokine storm, i.e. excessive production of TNF- α , IL-1, IFN- γ , and IL-6 etc., is involved in the pathogenesis of MAS, but its etiology has not been elucidated. Thus, it is difficult to discuss the potential induction of MAS by MRA. However, the following possibilities can not be ruled out: When treatment with MRA has to be deferred or discontinued, the primary disease is exacerbated, which induces MAS; infections develop during treatment with MRA, which induces MAS; and inhibition of IL-6 signal transduction by MRA has some effects on TNF- α , IL-1, and IFN- γ etc., which induces MAS. Concerning the use of MRA in patients with MAS, there is no evidence that the inhibition of IL-6 alone can control the condition of MAS and it is also envisaged that the clinical symptoms and laboratory findings of MAS are mild during treatment with MRA, which makes appropriate treatment difficult. Therefore, MRA should not be initiated in patients with MAS and even if MAS develops during treatment with MRA, treatment of MAS (steroid pulse therapy or cyclosporine etc.) should be initiated promptly and the administration of MRA should be interrupted until recovery from MAS. Relevant caution statements will also be included in the package insert etc.

PMDA considers that it is necessary to collect information and carefully examine the potential induction of MAS by MRA. There is no objection to the opinion that if MAS develops during

treatment with MRA, MRA should be discontinued and MAS should be treated first. However, regarding the administration of MRA after recovery from MAS, a stronger caution should be provided, e.g. contraindication, in view of a fatal course of MAS. This point will be discussed with the expert advisors.

e. Lipid metabolism abnormalities

Since increased lipid parameters following treatment with MRA have been noted, e.g. increased blood cholesterol was observed in 45.8% (275 of 601 subjects) of the Japanese adult RA safety population, PMDA asked the applicant to discuss the mechanism of lipid metabolism abnormalities associated with MRA and show their view on the possibility that such events increase the risk of cardiovascular events.

The applicant explained as follows:

Although no abnormal lipid parameters were noted in non-clinical studies of MRA, there are published articles reporting that treatment of human hepatocyte-derived HEP G2 cells with IL-6 results in decreased triglycerides and cholesterol etc. in the cells (Ettinger WH, et al. *Arterioscler Tromb.* 1994;14:8-13) and that the administration of rhIL-6 to rhesus monkeys results in decreased total cholesterol (Ettinger WH, et al. *J Gerontol A Biol Sci Med Sci.* 1995;50:M137-M140). Therefore, decreased lipid parameters due to increased IL-6 associated with the primary disease may have been elevated by the administration of MRA in clinical studies. In Japanese comparative studies for RA, the mean total cholesterol, LDL cholesterol, and triglycerides were increased following the initiation of MRA, but were all stable at around the upper limit of normal after Week 12. Furthermore, the relationship between the time course of lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, Atherogenic index) and the timing of onset of the event in 6 subjects who developed ischemic heart disease in the Japanese RA safety population was investigated. As a result, it was difficult to assess the relationship in 1 subject who developed the event after the 1st infusion of MRA, whereas the other 5 subjects all had increased lipid parameters (total cholesterol, triglycerides, LDL cholesterol, etc.) following treatment with MRA, but none of them showed extremely high values continuously up to the time of onset of the event. In addition, 1 subject had pre-existing coronary artery stenosis and 3 subjects were high-risk patients with coronary artery risk factors. Therefore, there seems no clear relationship between the onset of cardiovascular events and increased lipid parameters following treatment with MRA in these cases. Taking account of these findings, we consider at present that there is no trend towards an increased risk of cardiovascular events associated with MRA.

PMDA accepts the above response at present. However, in RA patients, corticosteroids, though at a low dose, are used frequently and hyperlipidemia has been reported as an adverse reaction to corticosteroids and it has been indicated that RA itself may be a coronary artery risk factor (Solomon DH, et al. *Circulation*. 2003;107:1303-7). Taking account of these points, the possibility that a combination of abnormal lipid parameters associated with MRA and these risk factors may increase the risk of cardiovascular events can not be ruled out. Therefore, the effects of MRA on the occurrence of cardiovascular events should continue to be investigated carefully and a long-term investigation via post-marketing surveillance etc. is necessary.

f. Pleurisy

Since pleurisy has been reported in 5 subjects in the Japanese RA safety population, PMDA asked the applicant to explain their view on its relationship with MRA.

The applicant explained as follows:

A definitive diagnosis has not been made for 3 of these 5 subjects. However, based on the clinical findings and clinical course, it seems that 2 subjects had pleurisy associated with RA and 1 subject had drug-induced BOOP, and the details are unknown for the remaining 2 subjects (However, one subject was treated with corticosteroids and was likely to have pleurisy of non-infectious cause and the other subject was treated with antibiotics only, so it seems that this subject had infections). Although the relationship to MRA is unclear, taking into account that a case suspected of non-infectious pleurisy has been reported, when pleurisy occurs during treatment with MRA, differentiating infectious pleurisy from non-infectious pleurisy is important. Therefore, a relevant caution statement will be included in the “Important Precautions” section of the package insert.

PMDA considers as follows:

Although pleurisy as a complication of rheumatoid arthritis is an event commonly observed in clinical practice as rheumatoid lung (Koopman W J, et al. *Arthritis and Allied Conditions 14th ed.* p1113-1114), the possibility that the above event was caused by effects of the formation of the immune complexes of MRA with free IL-6 receptor and complement activation can not be ruled out.

In addition, taking also into account that “type III immune complex mediated reaction” has occurred in 6 subjects (6 events) in the Japanese and foreign safety population though causality is unknown, attention should also be paid to a possible occurrence of a new autoimmune disease associated with MRA and information needs to be collected via post-marketing surveillance.

g. Cardiac disorders

Taking into account that cardiac disorders such as serious arrhythmia and ischaemic heart disease have been reported in the RA safety population, PMDA asked the applicant to explain their view on its relationship with MRA.

The applicant explained as follows:

Of the 1110 Japanese and foreign subjects included in the safety population, 14 subjects experienced serious cardiac disorders (15 events) (Japanese RA, 10 subjects/11 events; foreign RA, 3 subjects/3 events; Japanese sJIA, 1 subject/1 event) and a causal relationship could not be denied for the 5 events (angina pectoris, acute myocardial infarction, ventricular tachycardia, palpitations, and acute coronary syndrome, one case each) occurring in the Japanese RA patients, but many of these subjects had prior or concurrent heart disease or hypertension. Therefore, we think that the relationship to MRA is unclear at present, but taking account of the occurrence of serious events for which a causal relationship could not be denied, it will be stated in the “Important Precautions” section of the package insert that prior to treatment with MRA, electrocardiography should be performed as appropriate and when MRA is administered to patients with heart disease, electrocardiography should be performed periodically. In addition, the incidence of cardiac disorders will be identified via post-marketing surveillance.

PMDA largely accepted the above response.

h. Risk of gastrointestinal perforation

In ongoing foreign clinical studies, cases of gastrointestinal perforation have been accumulated, the investigator’s brochure etc. have been revised, and inquiries have been made from overseas regulatory authorities. Thus, PMDA asked the applicant to explain their view on its relationship to MRA and the necessity of including a caution statement in the package insert etc.

The applicant explained as follows:

Of a total of 4490 subjects in the safety population consisting of 945 Japanese and foreign RA subjects and 3545 subjects from Roche studies, 14 subjects experienced gastrointestinal perforation (15 events) (upper gastrointestinal perforation, 5 subjects/5 events; lower gastrointestinal perforation, 10 subjects/10 events). The 5 subjects with upper gastrointestinal perforation had risk factors other than MRA, i.e. antacid was not administered in spite of the use of NSAIDs and corticosteroids (4 subjects) and an endoscopy was performed (1 subject). Therefore, at present, it seems unlikely that MRA was its direct cause. On the other hand, of the

10 subjects with lower gastrointestinal perforation, as 1 subject had Crohn's disease and also underwent an endoscopy, lower gastrointestinal perforation in this subject was likely to be a secondary event, and the other 9 subjects all received concomitant NSAIDs or corticosteroids (7 of them received both) and in view of reports that lower gastrointestinal lesions such as ulcer and colitis occurred following the use of NSAIDs or corticosteroids in RA patients (Matsumoto T, et al. *Stomach and Intestine*. 2000;35:1147-1158, Bombardier C, et al. *N Engl J Med*. 2000;343:1520-1528, Laine L, et al. *Gastroenterology*. 2003;124:288-292) and that sigmoid diverticular abscess perforation is strongly associated with corticosteroids (Mpofu S, et al. *Ann Rheum Dis*. 2004;63:588-590) etc., all of them had risk factors. However, taking into account that 7 of 10 subjects had diverticular perforation (sigmoid colon, 3 events; other large intestine, 4 events), the possibility that the risk of infections associated with MRA worsened diverticulitis, leading to perforation, can not be ruled out. Based on the above, we consider that a special caution statement about upper gastrointestinal perforation is unnecessary at present. Cautions as to lower gastrointestinal perforation will be advised, including stating in the package insert that the product should be administered with care in "patients with diverticula of the intestinal tract", since patients with diverticula are likely to develop diverticulitis essentially, and also stating in the "Important Precautions" section that if abdominal pain/pyrexia etc. occur and diverticulitis/perforation are suspected, appropriate measures should be taken by conducting abdominal X-ray and CT tests, etc.

PMDA considers that although there are no major problems with the causality assessment of gastrointestinal perforation and the proposed caution statements at present, as gastrointestinal perforation is a serious event that could lead to death, it is necessary to collect information including the background factors etc. via post-marketing surveillance etc. and assess the relationship to MRA carefully.

i. Malignancy

PMDA asked the applicant to sort out subjects who developed malignancy following treatment with MRA and explain their view on the risk of malignancy associated with MRA.

The applicant explained as follows:

In a total of 4490 RA subjects in the safety population consisting of 945 Japanese and foreign RA subjects and 3545 subjects from Roche studies (excluding the placebo groups, but including subjects for whom the blind is maintained), all malignancies reported regardless of causality were 57 solid tumors and 2 blood cancers (of which 14 solid tumors and 2 blood cancers were reported in Japanese subjects). Commonly reported solid tumors were breast cancer (10

subjects), lung cancer (9 subjects), and uterine cancer (8 subjects) etc. In sJIA patients, 1 event of acute myeloid leukaemia (compassionate use) has been reported in Japan, but a causal relationship has been denied. In pJIA patients, no cases of malignancy have been reported in Japan or overseas to date. When the incidence of malignancy was compared between the above-mentioned 4490 Japanese and foreign RA patients and a Swedish large RA patient cohort,²¹ the overall incidence of solid tumors was significantly lower in the MRA studies (the ratio of the incidence in the MRA studies [8.21event (E)/1000 patient-year (PY)] to the incidence in the RA cohort [11.37E/1000 PY] [95% confidence interval]: 0.722 [0.556-0.938]). When analyzed by cancer type, though the data should be carefully interpreted due to a limited number of cases with each cancer type, there were no significant differences except for uterine cancer (the ratio of the incidence in the MRA studies [1.15E/1000PY] to the incidence in the RA cohort [0.39E/1000PY][95% confidence interval]: 2.925 [1.429-5.988]). Also as to uterine cancer, the affected sites in the 8 subjects in the MRA studies were uterine body cancer (1 subject), cervical cancer (5 subjects) (including 1 subject with cervical squamous cell carcinoma), and unknown (2 subjects), showing no consistent trend, and of whom, 1 subject with cervical cancer and 1 subject with unknown site are currently participating in a double-blind study and their treatment groups are unknown, and thus it is too early to discuss its risk. Therefore, although malignancies have been reported as adverse events, there is no clear evidence suggesting the risk of malignancy associated with MRA at present.

The applicant also responded as follows:

The occurrence of malignancies will be identified via post-marketing surveillance etc. and the relationship between MRA and malignancies will further be investigated.

PMDA considers as follows:

Although there is no objection to the applicant's view that the risk of malignancy associated with MRA is unclear at present, it is necessary to clarify the relationship via large, long-term investigations in Japan and overseas in future.

²¹ A study of the incidence of malignancy in 53067 patients diagnosed with RA up to 2003 including 4160 patients treated with anti-TNF preparation.

4.(iii).B.(3).2) Additional safety data from foreign clinical studies etc.

PMFDA asked the applicant to present the safety information from foreign clinical studies etc. for RA, pJIA, and sJIA that were ongoing at the time of submission or were initiated after submission, compare it with the safety information submitted with the application and during the regulatory review, and explain whether there are any differences in the safety profile.

The applicant explained as follows:

Clinical studies for RA, pJIA, and sJIA that were ongoing at the time of submission or were initiated after submission are shown in the following Table A. Deaths and serious adverse events reported as of September 2007 are presented in the following Table B based on the “MRA safety population” (a total of 4667 patients [RA, 4502 patients; pJIA, 19 patients; sJIA, 146 patients]), which is pooled from the “initial safety population” from the Japanese and foreign studies submitted with the application and during the regulatory review (1110 patients [RA, 945 patients; pJIA, 19 patients; sJIA, 146 patients]) and the studies in the following table A, and compassionate use patients and patients with diseases other than RA, pJIA, and sJIA (about 200 patients).

Table A. Description of major Japanese and foreign clinical studies contributing the additional safety information

Study population	Study no.	Study Design	Study treatment	No. of subjects	Duration of treatment
RA	WA17822 Overseas	Double-blind, comparative (placebo, different doses) in combination with MTX	Placebo, 4, 8 mg/kg Every 4 weeks	P group: 204 4 group: 212 8 group: 206	24 weeks
RA	WA17823 Overseas	Double-blind, comparative (placebo, different doses) in combination with MTX followed by an open-label study	Double-blind phase Placebo, 4, 8 mg/kg Every 4 weeks Open-label phase 8 mg/kg Every 4 weeks	P group: 392 4 group: 399 8 group: 399	Double-blind phase: 52 weeks Open-label phase: 1 year (52 weeks)
RA	WA18062 Overseas	Double-blind, comparative (placebo, different doses) in combination with MTX	Placebo, 4, 8 mg/kg Every 4 weeks	P group: 160 4 group: 163 8 group: 175	24 weeks
RA	WA18063 Overseas	Double-blind, comparative placebo-controlled in combination with DMARDs	Placebo, 8 mg/kg Every 4 weeks	P group: 414 MRA group: 802	24 weeks
RA	WA17824 Overseas	Main study: Double-blind, comparative MTX-controlled Sub-study: Double-blind, comparative MTX-controlled Placebo-controlled	Main study MRA 8 mg/kg group MTX group Sub-study MRA 8 mg/kg group MTX group Placebo group Every 4 weeks	Main study MRA group: 288 MTX group: 284 Sub-study MRA group: 92 MTX group: 88 Placebo group: 101	Main study 24 weeks Sub-study 24 weeks
RA	WA18695 Overseas	Open-label (long-term treatment study) Extension study of WA17822	8 mg/kg Every 4 weeks	2439 in both studies combined	264 weeks (ongoing)
RA	WA18696 Overseas	Open-label (long-term treatment study) Extension study of WA18062, WA18063, and WA17824	8 mg/kg Every 4 weeks		264 weeks (ongoing)
RA	MRA225JP Japan	Open-label	Up to 8 mg/kg Every 4 weeks	Target: 20	≥1 year

Table B. Deaths and serious adverse events in the Japanese and foreign safety populations

	Japanese RA and pJIA safety population	Foreign RA safety population	Japanese and foreign sJIA safety population	Diseases other than RA, pJIA, and sJIA
No. of deaths	4	28	4	10
Name of event (Events for which a causal relationship can not be denied are underlined)	<p>[Study MRA009JP] <u>EB virus infection</u></p> <p>[Study MRA214JP] <u>Pulmonary fibrosis/ bronchopulmonary aspergillosis, gastric cancer</u></p> <p>[Study MRA225JP] Renal function aggravated/cardiac failure</p>	<p>[Study WA17823] Bronchopneumonia, subarachnoid haemorrhage, sepsis, <u>gastrointestinal infection, pulmonary embolism</u></p> <p>[Study WA17824] Cardio-respiratory arrest, <u>gastrointestinal perforation, myocardial ischaemia</u></p> <p>[Study WA18063] <u>Mediastinitis/sepsis, haemorrhagic stroke</u></p> <p>[Study WA18695] <u>Gastric cancer, myocardial infarction, acute myocardial infarction</u></p> <p>[Study WA18696] Cardiac failure, <u>death, idiopathic progressive polyneuropathy, diverticular perforation/intestinal ischaemia, beta haemolytic streptococcal infection, chronic obstructive pulmonary disease, myocardial infarction, myocardial infarction, acute renal failure, completed suicide, septic shock, bacterial bronchitis, pneumonia</u></p> <p>[Study LRO300] Myocardial ischaemia</p> <p>[Study LRO301] Lung neoplasm malignant</p>	<p>[Study MRA324JP] <u>Haematophagic histiocytosis, cardiac amyloidosis</u></p> <p>[Compassionate use] Acute myeloid leukaemia, juvenile arthritis (both in Japan)</p>	<p>[Compassionate use] <u>Cardiac failure</u> (Japan), multiple myeloma (overseas), <u>death</u> (overseas), <u>cardiac failure</u> (overseas)</p> <p>[Study MRA006JP (Japan)] Myelodysplastic syndrome</p> <p>[Study LRO310 (overseas)] Acute renal failure, sepsis, mouth haemorrhage/asthenia, neurological symptom/pneumonia/cholecystitis, paraparesis</p>
Serious adverse events	866 patients/1300 events		59 patients/106 events	55 patients/108 events
Serious adverse drug reactions	341 patients/452 events		40 patients/70 events	23 patients/35 events
Main serious adverse drug reactions (No. of events)	Pneumonia (52), cellulitis (28), herpes zoster (19), urinary tract infection (7), diverticulitis (6), bacterial arthritis (6), sepsis (6), pyelonephritis (5), interstitial lung disease (5), bronchitis (5), osteomyelitis (5), neutropenia (5), etc.		Pneumonia (8), arthritis (4), ALT increased (4), AST increased (4), etc.	gastrointestinal haemorrhage (2), hepatic function abnormal (2), cellulitis (2), etc.

When the Japanese and foreign “initial safety population” (1110 patients) was compared with the “MRA safety population” (4667 patients), (a) The incidence of serious adverse events in RA patients was 264.6 and 186.6 E/1000PY, respectively, and the System Organ Classes reported at a higher incidence in the Japanese and foreign RA “initial safety population” compared to the “MRA safety population” were “Infections and infestations” (64.0 and 48.5 E/1000PY, respectively), “Immune system disorders” (5.0 and 2.6, respectively), “Eye disorders” (5.5 and 1.9, respectively), “Hepatobiliary disorders” (6.6 and 3.5, respectively), “Skin and subcutaneous tissue disorders” (5.0 and 2.2, respectively), “Musculoskeletal and connective tissue disorders” (57.5 and 24.1, respectively), “Investigations” (15.6 and 4.9, respectively), and “Injury, poisoning and procedural complications” (29.7 and 19.3, respectively). On the other hand, the System Organ Classes reported at a higher incidence in the “MRA safety population” were “Cardiac disorders” (7.1 and 10.4, respectively) and “Vascular disorders” (3.0 and 6.1, respectively). (b) The incidence of serious adverse events in pJIA patients was 134.0 E/1000PY in the “initial safety population” and 132.4 E/1000PY in the “MRA safety population”, showing no differences, and the incidences by System Organ Class were also similar. (c) The incidence of serious adverse events in sJIA patients was 392.1 E/1000PY in the “initial safety population” and 385.2 E/1000PY in the “MRA safety population”, showing no differences, and when analyzed by the System Organ Class, the incidence of “Eye disorders” (8.5 and 28.1 E/1000PY, respectively) was higher in the “MRA safety population”. Thus, although there were differences in the incidences of serious adverse events by System Organ Class, no noteworthy adverse events were observed and there should be no major differences in the safety profile between the “initial safety population” and “MRA safety population”.

PMDA asked the applicant to explain whether there is any information to be incorporated into the package insert for Japan based on the additional safety data from foreign clinical studies etc.

The applicant explained as follows:

(a) In foreign clinical studies, transaminases increased more frequently in the MRA+DMARD (mainly MTX) combination therapy group compared to the MRA monotherapy group, which seems attributable to a higher dose of concomitant MTX used in foreign studies compared to Japanese studies, but as it is envisaged that MRA will be used in combination with DMARDs after the market launch also in Japan, it will be stated in the “Important Precautions” section that when the product is used in combination with drugs that may induce liver injury or in patients with active hepatic disease or hepatic impairment, attention should be paid to the possible increase of transaminase value and it will be added in the “Other Precautions” section that a transient increase in transaminase value has been noted in foreign studies and its incidence was

higher in the MRA+DMARD combination therapy group compared to the MRA monotherapy group. (b) The incidence of neutropenia $<1.0 \times 10^9/L$ (Grade 3 or Grade 4) was 3.1% (9 of 287 subjects) in the MRA 8 mg/kg group and 3.4% (54 of 1579 subjects) in the MRA 8 mg/kg + DMARD group in foreign studies, which was higher in both severity and incidence compared to Japanese RA + pJIA studies (MRA 8 mg/kg group: 9 of 620 subjects). Although neutropenia was not particularly associated with the occurrence of serious infections, there were subjects with persistently low neutrophil counts, and also in Japan, there were a few subjects with persistently low neutrophil counts. Thus, it will be added in the “Adverse Reactions” section that transient neutropenia has been noted and persistent neutropenia \geq Grade 3 has been reported rarely. (c) Taking into account that 5 deaths due to infections for which a causal relationship can not be denied (gastrointestinal infection, pneumonia, mediastinitis/sepsis, bacterial bronchitis, beta haemolytic streptococcal infection, one case each) have been reported in foreign studies (one death due to EB virus infection in Japan), it will be added in the “WARNING” and “Clinically significant adverse reactions” sections that infections may run a fatal course.

PMDA considers that the above statements to be added to the package insert are appropriate. It is also necessary to pay an adequate attention to new safety data from foreign clinical studies and foreign post-marketing experience and take appropriate safety measures.

4.(iii).B.(3).3) Post-marketing safety measures

The possibility of the occurrence of adverse reactions to MRA including serious infections such as tuberculosis, effects on the cardiovascular system, and malignancy can not be ruled out and the long-term safety is unknown in many aspects. PMDA considers that it is essential to take post-marketing measures similar to those taken for TNF- α inhibitors, promoting the proper use and evaluating the safety of MRA. It is necessary to conduct a large-scale drug use investigation by registering doctors and all treated patients, and a long-term special survey to appropriately monitor patients including in terms of the occurrence of malignancy for at least 3 years, provide detailed data to healthcare professionals e.g. doctors, prepare a patient’s guide etc. describing the risks and benefits of MRA in an appropriate and easy-to-understand manner, and publish the information obtained after the market launch on the Internet etc. each time it becomes available. It is important to sort out and provide the information collected after the market launch to the clinical practice in order to facilitate the proper use of the product.

Regarding this point, PMDA has urged the applicant to develop a more detailed plan promptly and post-marketing safety measures will be further discussed also at the Expert Discussion.

III. Results of Compliance Review Concerning the Documents Appended to the New Drug Application and Conclusion by PMDA

(1) PMDA's conclusion on the results of document conformity audit

In the document compliance review conducted in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application, PMDA found no particular concerns and concluded that there should be no problem with conducting the regulatory review based on the submitted application dossier.

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

The GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application (5.3.5.2-RA-1, 5.3.5.4-RA-1, 5.3.5.1-RA-1, 5.3.5.4-RA-2, 5.3.5.2-sJIA-1, 5.3.5.1-RA-5, 5.3.5.1-RA-4, 5.3.3.4-1, 5.3.3.3-1, 5.3.5.1-sJIA-1, 5.3.5.2-RA-2). As a result, failure to notify the sponsor and the investigator in writing of the IRB's decision on the appropriateness of continuing the clinical study in response to serious and unexpected adverse drug reactions etc. informed by the sponsor and protocol deviations as to the administration method of the study drug were found at some medical institutions (the clinical study sites), but there were no major problems. Therefore, PMDA concluded that there should be no problem with conducting regulatory reviews based on the application dossier.

IV. Overall Evaluation by PMDA

Based on the submitted data, it is judged that the efficacy of MRA in the treatment of RA, pJIA, and sJIA has been demonstrated. The proposed statements in the "INDICATIONS" and "DOSAGE AND ADMINISTRATION" sections etc. of the package insert need to be further discussed. Regarding safety, since serious adverse drug reactions such as infections may occur, it is necessary to closely observe the patient's symptoms etc. and determine the risks/benefits prior to the use of MRA. The proposed caution statements about the occurrence of infections etc. in the package insert etc. also need to be further discussed. The conduct of a large-scale post-marketing survey (including a long-term special survey) is essential for MRA and it is necessary to provide the obtained information to doctors and patients etc. each time the information becomes available.

PMDA considers that the additional indications of RA, pJIA and sJIA for MRA may be approved if it can be concluded based on the results of the Expert Discussion that there are no particular problems.

Review Report (2)

January 22, 2008

Based on the results of the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) additionally reviewed the following points and took necessary actions. All the expert advisors attending the Expert Discussion have declared that they did not come under the Section 1 or 2 (1) of “Measures against the problem of conflict of interests involving the outside experts of the PMDA”, dated May 8, 2007, regarding the product submitted for registration.

1. Indications

PMDA judged that polyarticular-course juvenile idiopathic arthritis (pJIA) should be listed as a separate indication, instead of being implicitly included in the rheumatoid arthritis (RA) indication and that Tocilizumab (Genetical Recombination) (or MRA) should be indicated for patients who have responded inadequately to existing therapies also in the treatment of systemic juvenile idiopathic arthritis (sJIA), which was supported by the expert advisors. PMDA instructed the applicant to amend the indications as follows.

[Indications]

Treatment of the following diseases in patients who have had an inadequate response to existing therapies:

Rheumatoid arthritis (including the inhibition of progression of structural joint damage),
polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

The applicant accepted it.

2. Dosage and administration

PMDA judged that it is not appropriate to include in the dosage and administration section a recommendation to reduce the dosing interval in RA and pJIA patients with an inadequate response at the recommended dosage regimen, as there is no adequate scientific evidence that can assure the efficacy and safety of MRA at a reduced dosing interval. This judgment by PMDA was supported by the expert advisors.

On the other hand, a dosing interval reduction in sJIA patients was discussed taking also account of the opinion of the medical expert for the applicant: “sJIA is a severe disease presenting with systemic inflammatory symptoms and if the control of disease activity can not be sustained,

sJIA may be complicated by fatal macrophage activation syndrome (MAS). Therefore, the prevention of aggravation/flare of the condition is important in the treatment of sJIA and a dosing interval reduction is considered necessary to minimize the risk of flare of the condition associated with an inadequate dose of MRA.” As a result, it has been concluded that in light of the seriousness of sJIA, it is necessary to include a recommendation to reduce the dosing interval in the “DOSAGE AND ADMINISTRATION” section, as with in the case of Castleman’s disease. However, since a dosing interval reduction was attempted in a very limited number of subjects in clinical studies, it is necessary to adequately confirm the efficacy and safety of MRA at a reduced dosing interval via post-marketing surveillance. It is also necessary to clearly stipulate in the “Precautions for Dosage and Administration” section that the dosing interval should be reduced only when the improvement of symptoms is considered inadequate based on comprehensive assessment of disease activity, so that the dosing interval will not be reduced easily based on the CRP levels only.

3. Safety of MRA

Based on the results of the Expert Discussion, PMDA has concluded as follows regarding the necessity of further caution statements about tuberculosis, EB virus infection, and MAS etc.

1) Tuberculosis

Taking account of the occurrence of tuberculosis following treatment with MRA to date, it seems that the risk of tuberculosis relapse is not high with MRA compared to TNF inhibitors. However, since there are no sufficient data on the incidence of tuberculosis in long-term treatment and the incidence of tuberculosis among Japanese elderly is high etc., it has been concluded that the following measures should be taken, as with TNF inhibitors: Patients previously infected with tuberculosis should be listed in the “Careful Administration” section of the package insert; and it should be stated in the “Important Precautions” section of the package insert that whether or not the patient is infected with tuberculosis should be checked prior to the use of MRA. PMDA instructed the applicant to include these caution statements in the package insert and the applicant accepted it.

2) EB virus infection

It has been concluded that immunocompromised patients should be listed in the “Careful Administration” section of the package insert in order to cover latent infections and opportunistic infections etc., in addition to the proposed caution statements about infections, though a special caution statement about EB virus infection etc. is not required at present. PMDA instructed the applicant to include this caution statement in the package insert and the

applicant accepted it.

3) MAS

With respect to the necessity of restricting the use of MRA in sJIA patients after recovery from MAS (e.g. listing as a contraindication), the expert advisors commented that since the core of treatment after recovery from MAS is the prevention of relapse of MAS by controlling sJIA disease activity, restricting the use of MRA is not appropriate. Taking account of the comments, it has been concluded that no particular restriction is required at present. However, since MAS may be triggered by viral infections etc. besides the development of MAS associated with sJIA disease activity, caution is required in administering MRA in immunocompromised patients and the safety etc. of the use of MRA after recovery from MAS needs to be evaluated via post-marketing surveillance.

4. Post-marketing surveillance

Since serious adverse reactions to MRA have been reported, in view of the safety measures taken for TNF inhibitors (infliximab and etanercept), PMDA judged that a post-marketing survey over a certain period of time, covering all patients treated with MRA, should be conducted in order to ensure that the medical institutions are fully informed of the proper use of MRA and that adverse drug reaction information is captured, and instructed the applicant to take action accordingly.

The applicant responded that they will conduct a survey of all patients treated with MRA and explained about the survey as follows: (a) Analysis will be performed once 3000 cases have been collected for RA, but the survey will be continued until the final evaluation by the regulatory authority is obtained. (b) For pJIA and sJIA, the number of cases is not specified and analysis will be performed at an appropriate timing and the survey will be continued until the regulatory authority makes its final evaluation. (c) The product will not be delivered unless a written cooperation agreement for the survey has been obtained from the medical institution and measures will be taken to prevent a medical institution without the agreement from initiating MRA treatment in patients. (d) If MRA is delivered for the treatment of RA or JIA patients to the medical institutions to which MRA has already been delivered for Castleman's disease, we will give an advance explanation and request the control of the drugs to the pharmacy department so that MRA will not be administered to patients not registered for the survey. Until the agreement for the survey and patient registration, we will ensure that MRA will not be administered to patients other than the registered patients with Castleman's disease. (e) Each patient will be monitored for at least 6 months to detect the possible occurrence of adverse

events (the priority items: infections, gastrointestinal perforation, cardiac disorders, malignancy, infusion reactions, and lipid parameters, etc.) (f) Adverse drug reaction information collected from the survey will be summarized once a month and provided to the medical institutions.

PMDA also instructed the applicant to separately plan a long-term, specified drug use investigation of RA patients to identify the occurrence of malignancies and infections etc.

The applicant responded that they will conduct a long-term, specified drug use investigation where RA patients are monitored over 36 months and explore the occurrence of malignancies, cardiac disorders, and infections etc. and related factors.

PMDA considers that it is important to conduct these surveys promptly and evaluate the safety of MRA in details. PMDA has judged that the approval of MRA should be subject to the following conditions.

[Conditions for approval]

1. In post-marketing, conduct a drug use investigation, covering all patients treated with the drug, until data from a fixed number of patients will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.
2. Conduct a large-scale post-marketing survey with a comprehensive investigation of the safety of the drug, including the safety of long-term treatment with the drug and the occurrence of infections etc.

As a result of the above review, PMDA has concluded that the additional indications for MRA may be approved after modifying the indications and the dosage and administration as shown below, with the following conditions. Since the registered indication for MRA is Castleman's disease only and MRA is designated as an orphan drug for the indication of Castleman's disease, the appropriate re-examination period for the claimed indications should be 5 years 10 months. The 80 mg strength drug product and the 400 mg strength drug product are classified as both powerful drugs and biological products.

[Indications]

(a) Actemra 200 mg for Intravenous Infusion

- Treatment of the following diseases in patients who have had an inadequate response to existing therapies:
Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis
- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

(The underlined parts are additions to the current text)

(b) Actemra 80 mg / 400 mg for Intravenous Infusion

- Treatment of the following diseases in patients who have had an inadequate response to existing therapies:
Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis
- Improvement of various symptoms (e.g. generalised fatigue) and laboratory findings (increased C-reactive protein, increased fibrinogen, increased erythrocyte sedimentation rate, decreased haemoglobin, decreased albumin) associated with Castleman's disease. However, treatment with Actemra should be limited to patients for whom lymph node resection is not indicated.

[Dosage and administration]

(a) Actemra 200 mg for Intravenous Infusion

- Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.
- Systemic juvenile idiopathic arthritis, Castleman's disease
The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

(The underlined parts are additions to the current text)

(b) Actemra 80 mg / 400 mg for Intravenous Infusion

- Rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 4 weeks.

- Systemic juvenile idiopathic arthritis, Castleman's disease

The usual dosage is 8 mg/kg of Tocilizumab (Genetical Recombination) given as an intravenous infusion every 2 weeks. The dosing interval may be shortened to a minimum of 1 week according to the patient's symptoms.

[Conditions for approval]

For treatment of the following diseases in patients who have had an inadequate response to existing therapies:

Rheumatoid arthritis (including the inhibition of progression of structural joint damage), polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

1. In post-marketing, conduct a drug use investigation, covering all patients treated with the drug, until data from a fixed number of patients will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.
2. Conduct a large-scale post-marketing survey with a comprehensive investigation of the safety of the drug, including the safety of long-term treatment with the drug and the occurrence of infections etc.