Report on the Deliberation Results

August 13, 2015

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

[Brand name]	Remicade for I.V. Infusion 100
[Non-proprietary name]	Infliximab (Genetical Recombination) (JAN*)
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 30, 2014

[Results of deliberation]
In the meeting held on August 3, 2015, the Second Committee on New Drugs concluded that the partial changes for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

[Conditions for approval]
The applicant is required to develop a risk management plan and implement it appropriately.

**Japanese Accepted Name (modified INN)*

Review Report

July 22, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Remicade for I.V. Infusion 100
[Non-proprietary name]	Infliximab (Genetical Recombination)
[Name of applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 30, 2014
[Dosage form/Strength]	Powder for solution for infusion: Each vial contains 100 mg of lyophilized Infliximab (Genetical Recombination) to be reconstituted before use.
[Application classification]	Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage
[Items warranting special mention]	
	Orphan drug (Designation No. [*24 yaku*] 285, Notification No. 0913-5 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 13, 2012)
[Reviewing office]	Office of New Drug IV

Review Results

July 22, 2015

[Brand name]	Remicade for I.V. Infusion 100
[Non-proprietary name]	Infliximab (Genetical Recombination)
[Name of applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 30, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that a certain level of efficacy of the product in the treatment of intestinal-Behcet's disease, neuro-Behcet's disease, and vasculo-Behcet's disease can be expected, and its safety is acceptable in view of its observed benefits. Since the product was investigated in only a limited number of patients in clinical studies, the safety and efficacy should be further investigated in routine clinical practice after the market launch via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]
Treatment of the following diseases in patients who had an inadequate response to conventional therapies:
Rheumatoid arthritis (including prevention of structural damage to joint)
Refractory uveoretinitis associated with Behcet's disease
Plaque psoriasis, psoriatic arthritis, pustular psoriasis, erythrodermic psoriasis
Ankylosing spondylitis
Intestinal-Behcet's disease, neuro-Behcet's disease, vasculo-Behcet's disease
Treatment and maintenance therapy of Crohn's disease in the following patients (only in those who had an inadequate response to conventional therapies)
Patients with moderately to severely active Crohn's disease or
Patients with fistulizing Crohn's disease
Treatment of moderate to severe ulcerative colitis (only in patients who had an inadequate response to conventional therapies)

(Underline denotes added text.)

[Dosage and administration]
Rheumatoid arthritis
The usual dosage of infliximab is 3 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an inadequate or attenuated response at Week 6 or later, the dose may be increased or the dosing interval may be decreased in a stepwise manner. The dose may be increased up to 10 mg/kg at the dosing interval of 8 weeks or 6 mg/kg at a shorter dosing interval. The shortest dosing interval should be 4 weeks. Infliximab should be used in combination with methotrexate.

Refractory uveoretinitis associated with Behcet's disease
The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Psoriasis
The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Ankylosing spondylitis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 6 to 8 weeks thereafter.

Intestinal-Behcet's disease, neuro-Behcet's disease, vasculo-Behcet's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an inadequate or attenuated response at Week 6 or later, the dose may be increased to 10 mg/kg.

Crohn's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an attenuated response at Week 6 or later, the dose may be increased to 10 mg/kg.

Ulcerative colitis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Infliximab should be administered through an in-line filter with a microporous membrane of ≤1.2 μm.

(Underline denotes added text.)

[Conditions for approval]

The applicant is required to develop a risk management plan and implement it appropriately.

Review Report (1)

June 15, 2015

I. Product Submitted for Registration

[Brand name] Remicade for I.V. Infusion 100

[Non-proprietary name] Infliximab (Genetical Recombination)

[Name of applicant] Mitsubishi Tanabe Pharma Corporation

[Date of application] October 30, 2014

[Dosage form/Strength] Powder for solution for infusion: Each vial contains 100 mg of lyophilized Infliximab (Genetical Recombination) to be reconstituted before use.

[Proposed indication] Treatment of the following diseases in patients who had an inadequate response to conventional therapies:

Rheumatoid arthritis (including prevention of structural damage to joint)
Refractory uveoretinitis associated with Behcet's disease
Plaque psoriasis, psoriatic arthritis, pustular psoriasis, erythrodermic psoriasis
Ankylosing spondylitis
Intestinal-Behcet's disease
Neuro-Behcet's disease
Vasculo-Behcet's disease

Treatment and maintenance therapy of Crohn's disease in the following patients (only in those who have an inadequate response to conventional therapies):

Patients with moderately to severely active Crohn's disease or
Patients with fistulizing Crohn's disease

Treatment of moderate to severe ulcerative colitis (only in patients who had an inadequate response to conventional therapies)

(Underline denotes added text.)

[Proposed dosage and administration]

Rheumatoid arthritis

The usual dosage of infliximab is 3 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has inadequate or attenuated response at Week 6 or later, the dose may be increased or the dosing interval may be decreased in a stepwise manner. The upper limit of the single dose is 10 mg/kg at the dosing interval of 8 weeks and 6 mg/kg for a shorter dosing interval. The shortest dosing interval should be 4 weeks. Infliximab should be used in combination with methotrexate.

Refractory uveoretinitis in Behcet's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Psoriasis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Ankylosing spondylitis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 6 to 8 weeks thereafter.

Intestinal-Behcet's disease, neuro-Behcet's disease, vasculo-Behcet's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an inadequate or attenuated response at Week 6 or later, the dose may be increased to 10 mg/kg.

Crohn's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an attenuated response at Week 6 or later, the dose may be increased to 10 mg/kg.

Ulcerative colitis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Infliximab should be administered through an in-line filter with a microporous membrane of ≤1.2 μm.

(Underline denotes added text.)

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

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

Since this partial change application has been filed for approval of new indications, "data relating to quality" and "non-clinical data" have not been submitted.

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

Infliximab (Genetical Recombination) (hereinafter referred to as infliximab), the active ingredient of Remicade for I.V. Infusion 100 (hereinafter referred to as Remicade), is a chimeric anti-human TNFα monoclonal antibody discovered by Centocor, Inc. in the US (a predecessor of Janssen Biotech, Inc.). Infliximab comprises (i) the variable region derived from murine monoclonal antibody specific to human tumor necrosis factor (TNF)-α and (ii) the constant region derived from κ isotype of human IgG1. In Japan, Remicade was approved for the indication for Crohn's disease in January 2002, followed by additional approvals for the indications for the treatment of rheumatoid arthritis, refractory uveoretinitis associated Behcet's disease, psoriasis, ankylosing spondylitis, and ulcerative colitis.

Behcet's disease (BD) is a systemic inflammatory disease presenting recurrent orogenital aphthous ulcers, skin manifestations, eye manifestations, and genital ulcers as prominent symptoms, and the disease has a chronic course with recurring acute inflammation. The cause of BD is unknown. In Japan, BD is diagnosed according to 4 primary symptoms (recurrent orogenital aphthous ulcers, skin manifestations,[1] eye manifestations,[2] genital ulcer) and 5 secondary symptoms (arthritis without deformation or stiffness, epididymitis, gastrointestinal lesion represented by ileocecal ulcer, vascular lesion, and moderate to severe central nervous system lesion). The types of BD whose pathology is characterized by intestinal, central nervous system, and vascular lesion are defined as intestinal-BD,

[1] a, nodular erythematous rash; b, subcutaneous thrombophlebitis; c, folliculitis-like rash, acne-like rash

[2] a, iridocyclitis; b, uveoretinitis (chorioretinitis); c, if there are findings of posterior synechiae of iris, pigment deposition on the lens, chorioretinal atrophy, optic atrophy, complicated cataract, secondary glaucoma, and/or phthisis bulbi that occurred probably after (a) or (b), they are to be treated as the cases for (a) and (b).

neuro-BD, and vasculo-BD, respectively. BD with any of these lesions is considered to have a poor prognosis (Research Project on Overcoming Intractable Disease supported by Health and Labour Sciences Research Grants: Behcet's Disease Research Group. *Diagnostic criteria for Behcet's disease published by the Ministry of Health, Labour and Welfare* [with minor revision in 2010]).

There are no internationally established treatments for intestinal-, neuro-, or vasculo-BD, while in clinical settings in Japan, these diseases are treated with corticosteroids and immunosuppressants, among other drugs. However, since conventional therapies are sometimes insufficiently effective or cause adverse reactions precluding continued treatment, development of new treatment options has been desired.

It is reported that TNFα production was enhanced in peripheral blood monocytes and in the affected area of nodular erythematous rash in BD patients and in biopsy samples of intestinal tissue from patients with intestinal-BD, and that TNFα in the spinal fluid is increased in patients with neuro-BD, suggesting the involvement of TNFα in the pathology of BD. There are several reports on the treatment of BD with anti-TNF agents (Suzuki N, *Research on Behcet's disease supported by Health and Labour Sciences Research Grants [Research Project on Overcoming Intractable Disease], 2004 General Partial Research Report*. 2005;35-38; Suzuki N, et al., *Study on immune abnormality and inflammatory conditions in Behcet's disease; Research on Behcet's disease supported by Health and Labour Sciences Research Grants [Research Project on Overcoming Intractable Disease], 2005-2007 General Research Report*. 2008;43-51.).

Against this background, a petition was submitted from the "Behcet's Disease Research Group" supported by Health and Labour Sciences Research Grants (Research Project on Overcoming Intractable Disease) and from Hokkaido Behcet's Disease Patients Circle, requesting that intestinal-, neuro-, and vasculo-BD be included in the indications of Remicade. In the "Sixth Study Group on Unapproved and Off-label Drugs of High Medical Need" of the Ministry of Health, Labour and Welfare, it was concluded that Remicade (infliximab) was a drug of high medical need. Taking account of this, the Ministry of Health, Labour and Welfare requested in December 2010 that the applicant undertake the clinical development of Remicade for the relevant indication. The applicant started a clinical study of Remicade in patients with intestinal-, neuro-, and vasculo-BD in [redacted] 20[redacted] and, based on the results of the clinical study conducted in Japan by the applicant, submitted a partial change application to include additional indications.

Remicade (infliximab) was designated as an orphan drug in September 2012 with the expected indication of "Behcet's disease of special types (intestinal-, neuro-, vasculo-)" (Designation No. [*24 yaku*] 285, Notification No. 0913-5 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 13, 2012).

As of August 2014, Remicade is approved in 105 countries or regions, including Japan, but has not been developed for the treatment of intestinal-, neuro-, or vasculo-BD in other countries.

2. Non-clinical data

This application was submitted to add new indications. However, since no appropriate animal models are available for intestinal-, neuro-, or vasculo-BD, no new pharmacology study data have been submitted.

3. Clinical data

3.(i) Summary of biopharmaceutic studies and clinical pharmacology studies

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

As the evaluation data, the results from a Japanese clinical study in patients with intestinal-, neuro-, and vasculo-Behcet's disease (BD) were submitted.

Serum infliximab and anti-infliximab antibody (ATI) levels were measured by enzyme-linked immunosorbent assay (ELISA) (quantitation limit of serum infliximab, 0.1 μg/mL). The dose of Remicade is expressed in terms of infliximab.

3.(i).A.(1) Studies in patients

3.(i).A.(1).1) Japanese study (5.3.5.2.1, Study TA-650-23 [[redacted] to [redacted]])

In an open-label, uncontrolled study in 18 patients with intestinal-, neuro-, and vasculo-BD, Remicade (infliximab, 5 mg/kg) was administered as an intravenous infusion at Weeks 0 (the first dose), 2, and 6, and then every 8 weeks thereafter, to investigate pharmacokinetics. Patients meeting the dose increase criteria[3] at or after Week 30 were to receive infliximab at 10 mg/kg in the subsequent treatment period.

Infliximab (5 mg/kg) was administered as an intravenous infusion every 8 weeks to patients with intestinal-, neuro (acute and chronic progressive)-, and vasculo-BD to compare serum infliximab concentrations. Trough serum infliximab concentrations over time were as shown in Table 1. In 3 patients with intestinal-BD who received Remicade at an increased dose (10 mg/kg) at or after Week 30, trough serum infliximab concentrations before and at 8 weeks after the dose increase were 0.96 and 6.01 μg/mL, 4.39 and 9.77 μg/mL, and 7.78 and 18.74 μg/mL.

By Week 54, ATI was measured in all the 18 patients. As a result, ATI was positive in 0% of patients, negative in 5.6% (1 with intestinal-BD of 18 patients), and unevaluable in 94.4% (17 of 18 patients).

Table 1. Serum infliximab concentrations over time in patients with intestinal-, neuro-, or vasculo-BD in multiple intravenous infusion of Remicade (5 mg/kg) every 8 weeks (trough level, μg/mL)

	Week 14	Week 30	Week 54
Intestinal-BD	8.59 ± 4.53 (n = 11)	6.72 ± 3.98 (n = 11)	6.51 ± 3.96 (n = 8)
Neuro-BD	9.45 ± 4.09 (n = 3)	6.99 (n = 2)	7.95 (n = 2)
Vasculo-BD	8.86 ± 3.27 (n = 4)	4.95 ± 1.43 (n = 4)	5.62 ± 1.38 (n =4)
Total	8.79 ± 4.00 (n =18)	6.34 ± 3.46 (n = 17)	6.46 ± 3.42 (n = 14)

Mean ± standard deviation (number of patients)

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

PMDA asked the applicant to explain the relationship between serum infliximab concentration and clinical effect in patients with intestinal-, neuro-, or vasculo-BD.

The applicant explained as follows:

In the dose titration study in patients with rheumatoid arthritis (RA), maintaining trough serum infliximab concentrations by dose increase was critical for the maintenance of the efficacy, and the distribution of the improvement in RA assessed on the basis of the ACR criteria was analyzed by trough serum infliximab concentration. The results suggested that similar level of efficacy was achieved among patients in whom trough serum infliximab concentration was maintained at ≥1 μg/mL (*Review Report on Remicade for I.V. Infusion 100*, 2009). Also, it was reported that, in 27 patients with refractory uveitis associated with BD on treatment with infliximab, trough serum infliximab concentration was decreased after onset of ocular inflammation attacks compared with the level before the onset, with the cut-off level being 0.8 μg/mL (Ohno S, et al., *Research on Behcet's disease supported by Health and Labour Sciences Research Grants [Research Project on Overcoming Intractable Disease], 2013 General Partial Research Report*. 2014;51-55.).

In the Japanese study, the proportion of patients with a complete response by trough serum infliximab concentrations (<0.1 μg/mL, 0.1 to <1 μg/mL, 1 to <10 μg/mL, ≥10 μg/mL) at Week 30 was 0% (0 of 1 patient), 0% (0 of 0 patient), 69.2% (9 of 13 patients), and 66.7% (2 of 3 patients), respectively, precluding the clear elucidation of the relationship between trough serum infliximab concentrations and clinical effect because of the small number of patients with low trough serum infliximab concentrations (<1 μg/mL).

[3] Among patients in whom treatment effect against symptoms of intestinal-, neuro-, or vasculo-BD was confirmed by Week 30 based on clinical symptoms or morphological assessment, patients who showed attenuation of the efficacy and who required dose increase, as judged by a physician. In patients with chronic progressive neuro-BD or with vasculo-BD, if efficacy could not be evaluated by clinical symptoms or morphological assessment, IL-6 concentration in spinal fluid and inflammation markers were also to be used as references for evaluation.

PMDA considers as follows:
Because of the limited number of patients with intestinal-, neuro-, and vasculo-BD enrolled in the clinical study, it is impossible to draw any conclusion from the currently available data on the relationship between serum infliximab concentrations and efficacy in these BD patients. However, there was no trend toward a significant difference between the data from these patients and serum infliximab concentrations over time confirmed in patients with diseases for which indications of infliximab have been approved, suggesting that use of infliximab in patients with intestinal-, neuro-, or vasculo-BD will not pose any new concern from the clinical pharmacological point of view. However, attention should be paid to the efficacy in the case of the development of ATI which is suggested in patients treated with infliximab for other indications.

3.(ii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results of a Japanese study in patients with intestinal-, neuro-, or vasculo-BD (Study TA-650-23 [5.3.5.2.1]) were submitted. The dose of Remicade is expressed in terms of infliximab.

3.(ii).A.(1) Japanese study (5.3.5.2.1, Study TA-650-23 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of infliximab in patients with intestinal-, neuro (acute, chronic progressive)-, and vasculo-BD who are unresponsive or intolerant to conventional therapies such as corticosteroid to continue them[4] (target sample size, 15 [≥3 patients in each disease type]) at 21 centers in Japan [for pharmacokinetics, see "3.(i) Summary of biopharmaceutic studies and clinical pharmacology studies"].

Infliximab (5 mg/kg) was to be administered as an intravenous infusion at Weeks 0 (the first dose), 2, and 6, and then every 8 weeks thereafter up to Week 46. Patients meeting the dose increase criteria[3] at or after Week 30 were to receive Remicade at 10 mg/kg in the subsequent treatment period.

All of the 18 patients treated with infliximab (11 patients with intestinal-BD, 3 patients with neuro-BD [2 acute neuro-BD patients, 1 chronic progressive neuro-BD patient], 4 patients with vasculo-BD[5]) were included in the full analysis set (FAS), the safety analysis set, and the efficacy analysis set. Two patients discontinued the study (request of the patient [1 patient with neuro-BD], aggravation of the primary disease [1 patient with intestinal-BD]).

The primary efficacy endpoint was the percentage of patients with a complete response at 30 weeks after the start of treatment, among patients of each disease type (intestinal-, neuro [acute or chronic progressive]-, or vasculo-BD) and among all patients [Table 2]. As shown in Table 3, the percentage of patients with a complete response was 54.5% (6 of 11 patients) in patients with intestinal-BD, 33.3% (1 of 3 patients) in patients with neuro-BD, (0% in acute type [0 of 2 patients], 100% in chronic progressive type [1 of 1 patient]), 100% (4 of 4 patients) in patients with vasculo-BD, and 61.1% (11 of 18 patients) in all patients with 3 disease types combined. The percentage of patients with a complete response at Weeks 14 and 54, the secondary efficacy endpoints, is as shown in Table 3.

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4 Patients who met both of the following conditions: (a) Patients with diagnosis of complete or incomplete type and intestinal-, neuro-, or vasculo-BD according to "the diagnostic criteria for Behcet's disease established by the Ministry of Health, Labour and Welfare (with minor revision in 2010)," and (b) patients who have persisting lesion despite conventional therapies or could not receive conventional therapies because of intolerability. Each disease type had to meet all of the pre-determined inclusion criteria. Conventional therapies included corticosteroid, immunomodulators, aminosalicylic acids, metronidazole, and enteral nutrition for intestinal-BD; corticosteroid and immunomodulators for neuro-BD; and corticosteroid, immunomodulators, anticoagulants, and antiplatelet drugs for vasculo-BD.

5 One patient each with phlebothrombosis ranging from the inferior vena cava to the right popliteal vein, lower limb thrombophlebitis, right axillary artery occlusion, and left lower leg phlebitis associated with intractable ulcer.

6 Infusion reaction was defined as an adverse event that occurred during or within 2 hours after the administration of infliximab.

Table 2. Primary efficacy endpoint (definition of "complete response" in each disease type)

Disease type			Definition of complete response (All criteria should be met at the assessment)
Intestinal-BD			Clinical symptoms: Disappearance of the clinical symptoms of intestinal-BD Imaging findings (endoscopy): Ulcer at the lesion site has been cured or scarred compared with the conditions before treatment. No new active lesion is detected.
Neuro-BD	Acute	Patients presenting acute or subacute headache, pyrexia, and focal neurological symptoms at the enrollment	Clinical symptoms: Acute or subacute headache, pyrexia, and focal neurological symptoms observed before treatment have disappeared and not relapsed at the assessment time point. Imaging findings (head MRI): High intensity signal region has disappeared and is not detected again up to the assessment time point. Cell count and IL-6 concentration in spinal fluid: Both parameter levels decreased from baseline and the decreased levels are maintained up to the assessment time point.
		Patients presenting acute or subacute headache, pyrexia, and focal neurological symptoms twice or more within 1 year before enrollment	Clinical symptoms: Acute or subacute headache, pyrexia, and focal neurological symptoms do not last up to the assessment time point. Imaging findings (head MRI): High intensity signal region is not newly detected up to the assessment time point. Cell count and IL-6 concentration in spinal fluid: These parameter levels, if they exceeded the upper limit of the reference range at baseline, have improved after treatment and the decreased levels are maintained up to the assessment time point. If they were within the reference range at baseline, they do not exceed the upper limit of the reference range until the assessment time point.
	Chronic progressive		Clinical symptoms: Clinical symptoms of neuro (chronic progressive)-BD are not aggravated from baseline up to the assessment time point. Imaging findings (head MRI): No further atrophy of the brain stem from baseline is observed up to the assessment time point. IL-6 concentration in spinal fluid: IL-6 level decreased from baseline and the decreased level is maintained.
Vasculo-BD			Clinical symptoms: Clinical symptoms of vasculo-BD are not aggravated from baseline up to the assessment time point. Imaging findings (PET/CT, etc.): Aggravation from baseline is not observed up to the assessment time point. Inflammation markers (CRP, ESR[a)]): The marker levels decreased from baseline and the decreased levels are maintained.

a, CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate

Table 3. Percentage of patients with complete response by disease type at Weeks 14, 30, and 54 (FAS)

	Week 14[a]	Week 30[b] (primary endpoint)	Week 54[a]
Total	61.1 (11/18)	61.1 (11/18)	68.8 (11/16)
Intestinal-BD	54.5 (6/11)	54.5 (6/11)	60.0 (6/10)
Neuro (acute)-BD	0 (0/2)	0 (0/2[c])	0 (0/1)
Neuro (chronic progressive)-BD	100 (1/1)	100 (1/1)	100 (1/1)
Vasculo-BD	100 (4/4)	100 (4/4)	100 (4/4)

% (number of patients)
a, OC; b, LOCF; c, One of 2 patients discontinued the treatment before Week 30.

Adverse events were observed in 94.4% (17 of 18 patients) of patients. The incidence of adverse events by disease type was 90.9% (10 of 11 patients) in patients with intestinal-BD, 100% (3 of 3 patients) in patients with neuro-BD, and 100% (4 of 4 patients) in patients with vasculo-BD. Adverse events reported by ≥2 patients were as shown in Table 4. No death occurred. Serious adverse events were reported in 11.1% (2 of 18 patients), which were cataract in 1 patient (intestinal-BD) and Behcet's syndrome in 1 patient (intestinal-BD). A causal relationship to Remicade was ruled out for both events, and the events resolved eventually. There were no adverse events leading to study discontinuation.

Adverse drug reactions were observed in 66.7% (12 of 18 patients) of all patients with 3 disease types combined.

Table 4. Adverse events reported by ≥2 patients (safety analysis set, n = 18)

Double stranded DNA antibody positive	8 (44.4)
Upper respiratory tract infection	5 (27.8)
Nasopharyngitis	4 (22.2)
Gastroenteritis	2 (11.1)
Infective gastroenteritis	2 (11.1)
Headache	2 (11.1)
Proctalgia	2 (11.1)
Acne	2 (11.1)
Arthralgia	2 (11.1)
Back pain	2 (11.1)
Pyrexia	2 (11.1)
Antinuclear antibody increased	2 (11.1)
Ligament sprain	2 (11.1)

Number of patients (%)

3.(ii).A.(2) Japanese clinical practice guidelines, textbooks, etc.

3.(ii).A.(2).1) Consensus statement for the clinical practice of intestinal-Behcet's disease (Research Project on Overcoming Intractable Disease supported by Health and Labour Sciences Research Grants, 2013)

The following description is provided:

Anti-TNF-α agents are positioned as one of the standard treatments for intestinal-BD. If patients have severe local or systemic conditions or if deep ulcer is confirmed on endoscopy or roentgenography, remission induction therapy is performed by the administration of corticosteroid or by subcutaneous injection of Adalimumab (Genetical Recombination) at an initial dose of 160 mg (Week 0), followed by 80 mg at Week 2 and 40 mg at Week 4. If the treatment is effective, the treatment is switched to maintenance therapy with 40 mg subcutaneous injection once every 2 weeks. If infliximab (5 mg/kg) is used, infliximab is administered as an intravenous infusion at weeks 0, 2, and 6 and, if the treatment is effective, the subsequent treatment is switched to the maintenance regimen of once every 8 weeks thereafter.

3.(ii).A.(2).2) Clinical practice guideline for neuro-Behcet's disease (Research Project on Overcoming Intractable Disease supported by Health and Labour Sciences Research Grants, 2013)

The following description is provided:

The standard therapy for acute attacks of neuro-BD is moderate or high dose corticosteroid. In case of cyclosporine-induced acute neuro-BD, subsequent attacks are almost completely prevented by discontinuation of cyclosporine, whereas colchicine is recommended to prevent the attacks of acute neuro-BD not caused by cyclosporine. The preventive effect of Remicade awaits future studies.

In patients with chronic progressive neuro-BD, methotrexate (MTX) is the key drug and, when MTX is not sufficiently effective, infliximab (5 mg/kg) should be concomitantly administered.

3.(ii).A.(2).3) Proposed statement on clinical practice guideline for vasculo-Behcet's disease (Research Project on Overcoming Intractable Disease supported by Health and Labour Sciences Research Grants, 2014)

The following description is provided:

Corticosteroid and immunosuppressants are shown to contribute to the improvement of prognosis of patients with active vasculo-BD with inflammatory findings etc., and should therefore be actively used from the early stage of the disease. There are sporadic case reports on the efficacy of biological products. Thus, they are expected as treatment options for vasculo-BD.

3.(ii).A.(2).4) Today's Therapy, FY 2015 (2015;821-823)

The following description is provided:

Adalimumab is listed in the National Health Insurance Drug Price List for the treatment of intestinal-BD. However, for the treatment of refractory cases of intestinal-, neuro-, or vasculo-BD, concomitant use with MTX or with infliximab should be considered. Remicade (5 mg/kg) should be administered as an intravenous infusion over ≥2 hours at Weeks 0, 2, and 6, and then every 8 weeks thereafter.

3.(ii).A.(3) Foreign clinical practice guidelines, textbooks, etc.

3.(ii).A.(3).1) EULAR recommendations for the management of Behcet's disease (Hatemi G, et al., *Ann Rheum Dis.* 2008;67:1656-1662)

The following description is provided:

- Intestinal-BD

Although there is no evidence-based treatment, use of salazosulfapyridine, corticosteroid, azathioprine, thalidomide, or anti-TNF-α agents should be tried as treatment options before surgery. There are case reports showing the efficacy of anti-TNF-α agents in resistant cases.

- Neuro-BD

Although there are no controlled data, agents to be tried as options to treat brain parenchymal lesions include corticosteroid, interferon-α preparations, azathioprine, cyclophosphamide, MTX, and TNFα antagonists. Immunosuppressives may also be effective in preventing recurrences and progression. Interferon-α and anti-TNF-α agents have been used with some success in resistant cases.

- Vasculo-BD

Although there is no firm evidence, venous thrombosis associated with vasculo-BD is considered to be caused by the inflammation of the vascular wall, and immunosuppressives are used to suppress the inflammation. Also, immunosuppressives reduce the risk of post thrombotic syndrome and the relapse of deep vein thrombosis. It is reported that patients with peripheral artery aneurysm have a high risk of rupture and are indicated for surgical treatment, whereas patients on immunosuppressives generally have a low risk of recurrences. Patients with pulmonary artery aneurysm are treated mainly with immunosuppressives.

3.(ii).A.(3).2) Oxford Textbook of Vasculitis, 3rd ed. (2014;467-490)

The following description is provided:

- Intestinal-BD

5-Aminosalicylic acids and azathioprine, in combination with corticosteroid, suppress acute symptoms almost completely. However, in patients with refractory intestinal-BD, thalidomide and anti-TNF-α agents are effective. Infliximab, in particular, effectively cures ulcer and fistula, promptly improving abdominal pain and melaena and thereby leading to a long-term remission.

- Neuro-BD

Brain parenchymal lesions are treated with corticosteroid in combination with immunosuppressants (cyclophosphamide, azathioprine), and immunosuppressants are effective in preventing the relapse. There are case reports showing that infliximab is effective for brain parenchymal lesion resistant to other drugs.

- Vasculo-BD

Since venous thrombosis in BD is caused by the inflammation of the vascular wall, immunosuppressants are effective in preventing the relapse and progression to post thrombotic syndrome. In the case of serious conditions such as superior vena cava thrombosis and Budd-Chiari syndrome, use of cyclophosphamide is reported to be desirable, whereas infliximab was not effective. As for pulmonary artery aneurysm, treatment with immunosuppressants and corticosteroid is recommended. There are case reports showing the effectiveness of infliximab in the treatment of refractory pulmonary artery lesions.

3.(ii).A.(4) Descriptions in published literature

Using PubMed (search formula, “Infliximab” + “Behcet”) and Igaku Chuo Zasshi (search formula, “Infliximab [in Japanese]” + “Behcet [in Japanese]”) databases, a total of 252 and 286 reports, respectively, were retrieved, from which internal-, neuro-, or vasculo-BD related literature was selected (August 1, 2014).

3.(ii).A.(4).1) Intestinal-BD

Among literature related to intestinal-BD, 6 published reports on continuous administration of infliximab mostly for ≥1 year and 1 related report from the “Reports of the Behcet's Disease Research

Group" were submitted. The main contents of the reports are as shown below.

No.	Source literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
1	Saito K., *Research on Behcet's disease supported by Health and Labour Sciences Research Grants (Research Project on Overcoming Intractable Disease), 2013 General Partial Research Report,* 2014;69-72.	Japan	Patients with intestinal-BD with active ulcer resistant to conventional therapies (21)	3 to 5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter for 3 years If no sufficient response was obtained, the dose was increased (to 3-6 mg/kg) or the dosing interval was decreased (to 4-8 weeks).	Ulcer-healing rate was 66.7%, as assessed by endoscopy of the lower gastrointestinal tract. The mean DAIBD score[a] decreased from 1 year after the start of treatment (73.3 at baseline, 21.4 after 1 year, 11.1 after 2 years, 11.7 after 3 years). The treatment was continued for 3 years in 85.7% of patients, and was discontinued in 3 patients because of poor response. Infliximab was administered at an increased dose or at shorter intervals in 13 patients. In 1 of 3 patients with relapse, the disease was controllable by an increased dose or decreased dosing intervals. From 2 years after the start of treatment, the amount of corticosteroid used decreased.	Mild infection (e.g., viral infection, cystitis, tonsillitis, bronchitis) was observed in 15 patients. There were no serious adverse events or no treatment discontinuation due to adverse events.
2	Kinoshita H et al., *Intern Med*. 2013;52:1855-1862	Japan	Patients with fulminant (serious abdominal pain or gastrointestinal haemorrhage) intestinal-BD (4), patients with intestinal-BD with active ulcer resistant to conventional therapies (10), and patients with intestinal-BD for whom corticosteroid was contraindicated (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter (One patient received only a single dose)	Of 11 patients whose follow-up was possible at 12 months after the start of treatment, 64% (7 of 11 patients) showed improvement and 27% (3 of 11 patients) achieved remission (including 1 patient receiving only a single dose). Of 8 patients whose follow–up was possible at 24 months after the start of treatment, 4 patients (50%) showed improvement and 3 patients (38%) achieved remission. Relapse occurred in 1 patient at 2 years after the start of treatment. Remission was maintained for another 2 years in this patient by decreasing the dosing interval to 4 weeks. In 5 of 7 patients who showed improvement at 12 months after the start of treatment, the dose reduction of corticosteroid was possible at 12 months after the start of treatment.	Infusion-related reaction and pyrexia occurred in 1 patient each.
3	Iwata S et al., *Mod Rheumatol.* 2011;21:184-191	Japan	Corticosteroid-dependent or contraindicated patients with intestinal-BD with active ulcer resistant to conventional therapies (10)	3 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter for 2 years If no sufficient response was obtained, 5 mg/kg was allowed to be administered every 6 weeks.	The rate of ileocecal ulcer disappearance was 50% (5 of 10 patients) at 6 months after the start of treatment and 90% (9 of 10 patients) after 12 months. Improvements in clinical symptoms, CT findings, CRP, and ESR were observed in 100% (10 of 10 patients) of patients. Relapse occurred in 2 patients (after 4 weeks in 1 patient, after 4 months in 1 patient), but improved after administration at 5 mg/kg every 6 weeks. Treatment was discontinued in 1 patient after a 2-year remission, and remission was maintained for another 1 year. Five patients received corticosteroid concomitantly at the start of treatment, but the dose reduction of corticosteroid was possible in all of them (22.0 mg/day before the start of treatment, 1.8 mg/day at 24 months after the start of treatment).	No serious adverse events were observed.

No.	Source literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
4	Naganuma M et al., *Inflamm Bowel Dis.* 2008;14:1259-1264	Japan	Patients with fulminant intestinal-BD resistant to conventional therapies and dependent on corticosteroid (6)	5 mg/kg at Weeks 0, 2, and 6, and then every 6 to 8 weeks thereafter	Remission was observed in 4 of 6 patients (duration of remission: 9, 10, and 16 months, and 3 years [administration: every 6 to 8 weeks]). Two patients did not show a response, requiring surgical treatment. In one of them, remission was maintained by continuous administration for 2 years after surgery.	Not available
5	Maruyama Y et al., *Intern Med.* 2012; 51:2125-2129	Japan	Patient with intestinal-BD resistant to corticosteroid and 6-MP treatment (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter (for 6 years)	Marked improvement in clinical symptoms, CRP, and ileocecal ulcer was observed at Week 6, and scarring of the ulcer was observed after 8 months. Remission was maintained for 6 years by the administration of infliximab alone. It was possible to discontinue corticosteroid.	No adverse events
6	Tsujisaki M et al., *Internal medicine.* 2012;110:149-152	Japan	Patient with intestinal-BD resistant to treatment with azathioprine, mesalazine, and colchicine (1)	200 mg at Weeks 0, 2, and 6, and then every 8 weeks thereafter (for 2 years)	Improvement of clinical symptoms, normalization of CRP, and scarring of ileocecal ulcer were observed. Remission was maintained for 2 years.	Not available
7	Kaneko U et al., *Jpn J Clin Immunol.* 2010;33: 157-161	Japan	Patient with intestinal-BD resistant to treatment with corticosteroid, MTX, and cyclosporine (1)	4 mg/kg at Weeks 0, 2, 4, and 8, and then every 8 weeks thereafter	Marked improvement in clinical symptoms and decreases in CRP and ESR were observed at Week 4. Improvement in ulcer was confirmed on imaging findings after 8 months, and remission was maintained for ≥1 year. The dose reduction of corticosteroid was possible.	No adverse drug reactions

a: DAIBD (Disease Activity Index for Intestinal Behcet Disease): a disease activity score (Cheon JH, et al., *Inflamm Bowel Dis*. 2011;17:605-613)

3.(ii).A.(4).2) Neuro-BD

Among literature related to neuro-BD, 14 published reports mainly describing the dose were submitted. The main contents of the reports are as shown below.

No.	Source literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
1	Pipitone N et al., *Arthritis Rheum.* 2008;59:285-290	Italy	Patients with neuro-BD with the following lesions/findings: Pontine ischemia (1), High-intensity T2-weighted signal in brain stem (1), Hemiparesis of right face, arm, and leg (1), Right brain stem lesion (1), High-intensity T2-weighted signal in right midbrain (1), High intensity signal in left temporal region and hippocampus (1), High-intensity T2-weighted signal in pons and midbrain (1), High-intensity T2-weighted signal in pons, cerebellar peduncle, and bulb (1)	5 mg/kg at Weeks 0, 2, and 6 (at Weeks 0, 1, 3, and 8 in 1 patient), and then every 8 weeks thereafter One patient received infliximab only at Weeks 0, 2, and 6.	Improvement in neural symptoms was observed in all patients. No change or improvement in brain stem lesion was observed in 6 of 8 patients, whereas results were unknown in 2 patients. The dose reduction of corticosteroid was possible in 3 patients.	No infliximab-related serious adverse events were reported.

No.	Source literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
2	Kikuchi H et al., *J Neurol Sci.* 2008;272:99-105	Japan	Patients with neuro-BD (chronic progressive) with lesions in midbrain, pons, and medulla (5)	5 mg/kg at Weeks 0, 2, 6, and 14 in combination with MTX (10-17.5 mg/week) and prednisolone (0-10 mg/day)	Improvement in symptoms was observed in 3 of 5 patients at Week 24. Aggravation of symptoms was not observed in any of the patients. A marked decrease in IL/6 concentration in the cerebrospinal fluid was observed in 5 of 5 patients (1/2 to 1/37).	Headache and asymptomatic *Pneumocystis* pneumonia in 1 patient each
3	Giardina A et al., *Rheumatol Int.* 2011;31:33-37	Italy	Patients with neuro-BD who had an inadequate response to conventional therapies (5)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Improvement in symptoms was observed in 5 of 5 patients, and remission lasted for 1 year in 3 of them. Infliximab was administered for 1 year in 3 of 5 patients and discontinued at Weeks 24 and 37 in the remaining 2 patients.	Headache and non-Hodgkin's lymphoma in 1 patient each
4	Kadowaki S et al., *Clinical Neurology.* 2011;51:261-266	Japan	Patient with neuro-BD who had an inadequate response to treatment with corticosteroid and MTX (1) High-intensity T2-weighted signal from left midbrain to thalamus	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Remission of clinical symptoms lasted for 1 year. IL-6 concentration in spinal fluid decreased, and the decreased level was maintained.	Not available
5	Matsui T et al., *Mod Rheumatol.* 2010;20:621-626	Japan	Patient with chronic progressive neuro-BD (1) High-intensity T2-weighted signal in pons	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Some of the symptoms improved and brain stem lesion disappeared almost completely. IL-6 concentration in spinal fluid decreased once and increased again (123 pg/mL after 6 months), and remained at an increased level (>100 pg/mL). Ataxia and urinary incontinence continued, but acute attack was not observed for ≥2 years.	Not available
6	Ribi C et al., *J Neurol Neurosurg Psychiatry.* 2005;76:1733-1735	Switzerland	Patient with neuro-BD with a single lesion in left thalamus to posterior limb of internal capsule (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Symptoms improved and brain stem lesion disappeared almost completely. Relapse occurred at 7 months after treatment discontinuation, but no new relapse occurred for 16 months after resumption of administration.	Treatment was well tolerated.
7	Alty JE et al., *Clin Neurol Neurosurg.* 2007;109:279-281	UK	Patient with neuro-BD with high-intensity T2-weighted signal in bilateral posterior limbs of internal capsule (1)	3 mg/kg every 8 weeks in combination with MTX (10 mg/week)	Frequency of neural symptoms decreased (before the start of treatment, symptoms lasted 1 to 2 weeks every 2 to 3 months, whereas symptoms occurred only twice in 3 years after the start of treatment)	Increased liver enzyme levels, resulting in discontinuation of infliximab (switched to etanercept [genetical recombination])

No.	Source literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
8	Abalos-Medina GM et al., *Int J Rheum Dis*. 2009;12:264-266	Spain	Patient with neuro-BD with high-intensity T2-weighted signal in left parietal white matter (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter.	Symptoms improved, and brain stem lesion disappeared almost completely. Remission was maintained even after 1 year.	Not available
9	Madanat WY et al., *Clin Exp Rheumatol.* 2008;26:S126-7	Jordan	Patient with neuro-BD with high intensity signal region in brain stem (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter in combination with MTX	Symptoms improved (neurologic symptoms improved within 1 week) and MRI findings normalized.	Aggravation of osteomalacia
10	Leccese P et al., *Clin Exp Rheumatol.* 2010;28:S102	Italy	Patient with neuro-BD with high intensity signal region in thalamus, right midbrain, and right anterior subcortical white matter (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter → every 5 weeks → adalimumab (genetical recombination)	Infliximab was administered to treat symptoms of uveitis. Uveitis improved but the patient experienced neuro-BD. Concomitant use with cyclosporine was discontinued, and infliximab alone was administered every 5 weeks. However, infliximab was switched to adalimumab because of the resistance to infliximab.	Not available
11	Fasano A et al., *J Neuroimmunol.* 2011;239:105-107	Italy	Patient with neuro-BD with multiple lesions in basal nucleus and in white matter in frontal and temporal lobe (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 6 weeks thereafter	Symptoms and brain stem lesion improved but, due to the relapse of uveitis, infliximab was administered every 6 weeks. Remission was maintained for the subsequent 4 years.	No adverse drug reactions
12	Kanemaru H et al., *J Dermatol.* 2013;40:632-634	Japan	Patient with neuro-BD with multiple lesions in middle temporal lobe, midbrain, and left cerebellum (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Symptoms improved. Brain stem lesion showed marked improvement (after 42 days). Remission was maintained for 2 years.	No adverse drug reactions
13	Uygunoğlu U et al., *J Spinal Cord Med.*[Epub ahead of print] 2014	US	Patient with lesion with high-intensity T2-weighted signal in a wide range from cervical spine to thoracic vertebrae (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Symptoms improved and lesions disappeared almost completely. Remission was maintained for 3 years.	Not available
14	Li J et al., *Intern Med J*. 2014;44:96-100	Australia	Patient with neuro-BD with lesions in pons, cervical spine, and thoracic vertebrae (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter → every 6 weeks Total treatment period, 56 months	Infliximab was administered every 6 weeks for treatment of paresis. Symptoms improved and brain stem lesion disappeared almost completely. Remission is continuing as of 56 months of treatment.	Well tolerated

3.(ii).A.(4).3) Vasculo-BD

Among literature related to vasculo-BD, 10 published reports mainly describing the dose were submitted. The main contents of the reports are as shown below.

No.	Published literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
1	Adler S et al., *Arthritis Care Res*. 2012;64:607-611	Switzerland	Patients with serious vasculo-BD with the following lesions: Aortic lesion (3), Pelvic venous thrombosis (1), Femoral artery/vein thrombosis (1), Retinal vasculitis (2)	3 to 5 mg/kg every 4 to 8 weeks	All patients showed improvement in systemic inflammation and decrease in CRP (mean, 89 mg/L → 9 mg/mL) within 5 days Two patients with retinal vasculitis achieved improvement in visual acuity. Improvement in graft patency and aortic dissection was observed. Administration of infliximab was discontinued in 2 of 7 patients.	No major infection or allergic reaction
2	Seyahi E et al., *Rheumatology.* 2007;46:1213-1214	Turkey	Patients with BD with severe Budd-Chiari syndrome (hepatic artery thrombosis) (3)	5 mg/kg	Infliximab was administered after the onset of hepatic encephalopathy, but the patient died.	Death
				3 mg/kg	Hepatic encephalopathy occurred after the start of treatment with infliximab, and the patient fell into hepatic coma and died 3 weeks later.	Death
				5 mg/kg	The size of the thrombus within the hepatic vein remained unchanged, while the thrombus within the inferior vena cava shrank.	After the second dose, severe headache and diplopia occurred. In addition, bilateral papillary congestion and intracranial venous sinus thrombosis occurred. These symptoms improved with administration of cyclophosphamide for 6 months after discontinuation of infliximab.
3	Rokutanda R et al., *Mod Rheumatol.* 2013;23:412-413	Japan	Patient with BD associated with hypertrophy of the aorta wall, common carotid artery wall, and left subclavian artery wall (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Laboratory values returned within the normal range within 2 months without the use of corticosteroid, and remission was maintained for another 6 months.	Not available
			Patient with BD associated with diffuse hypertrophy of the aortic wall (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Improvement in uveitis, intestinal symptoms, and aortic wall hypertrophy was observed without the use of corticosteroid. CRP and ESR improved to levels within the reference range. Remission was maintained for 1 year.	Not available
4	Endo LM et al., *Clin Rheumatol.* 2007;26:1537-1539	US	Patient with BD associated with oculocutaneous albinism, pulmonary artery aneurysms, and thrombi (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Symptoms were stabilized for 10 months.	Not available

No.	Published literature	Country	Study patients (No. of patients)	Dosage and administration	Efficacy	Safety
5	Baki K et al., *Ann Rheum* 2006;65:1531-1532	Switzerland	Patient with BD associated with haemoptoe and pulmonary artery aneurysms (1)	5 mg/kg for 14 months continuously	Symptoms improved within a few days. CRP decreased (from 227 mg/L to <10 mg/L), vasculitis improved, and thrombus disappeared. Remission was maintained for ≥2 years.	Not available
6	O'Leary EA et al., *Vasc Endovascular Surg.* 2011;45:98-102	US	Patient with BD associated with deep femoral artery aneurysm (1)	500 mg at Weeks 0 and 2	Surgical treatment was performed after improvement of symptoms.	Not available
7	Magro-Checa C et al., *Clin Exp Rheumatol.* 2013;31:S96-98	Spain	Patient with BD associated with myocardial infarction and right common iliac vein thrombosis (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter Re-treatment: 5 mg/kg at Weeks 0, 2, and 6, and then every 6 weeks thereafter	Infliximab was administered to treat ocular manifestation of BD, and remission was maintained for 3 years. At 4 months after discontinuation of infliximab for personal reasons, thrombus occurred. Administration of infliximab was resumed, and disappearance of the thrombus was confirmed at 2 months and 1 year after resumption.	Not available
8	Yoshida S et al., *Mod Rheumatol.* 2012;22:791-795	Japan	Patient with intestinal-BD complicated with repeated deep vein thrombosis of the leg and pulmonary embolism (1)	5 mg/kg at Weeks 0 and 2, and then every 4 weeks thereafter	After the administration of infliximab, CRP decreased (from 8.02 mg/dL to 0.14 mg/dL) and clinical symptoms improved. Shrinkage of venous thrombus was confirmed at 24 days after the start of treatment. Remission was maintained for 1 year.	No adverse drug reaction
9	Tolosa-Vilella C et al., *Clin Exp Rheumatol.* 2011;29:S94-95	Spain	Patient with BD complicated with bilateral multiple pulmonary artery aneurysms associated with vasculitis and thrombi, and with atrial thrombus (1)	5 mg/kg at Weeks 0, 2, 6, 14, and 22	Clinical symptoms and imaging findings improved at 15 days after the start of treatment. Pulmonary artery aneurysms shrank and atrial thrombus disappeared at 6 months after the start of treatment.	Not available
10	Schreiber BE et al., *Semin Arthritis Rheum.* 2011;41:482-487	UK	Patient with BD associated with pulmonary artery aneurysms (1)	5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks thereafter	Clinical symptoms and inflammatory reaction improved rapidly (CRP decreased below the lower detection limit). Pulmonary artery aneurysms disappeared. Remission was maintained for 30 months.	Not available

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

3.(ii).B.(1) Clinical positioning

Regarding the clinical positioning of Remicade (infliximab) in the treatment of intestinal-, neuro-, and vasculo-BD, PMDA confirmed, based on the data submitted by the applicant and on the latest clinical practice guidelines, and textbooks available in and out of Japan [see "3.(ii).A. Summary of the submitted data"], that the efficacy of infliximab, alone or in combination with MTX, has been demonstrated both in and out of Japan, and that the drug is therefore one of the treatment options for patients who had an inadequate response to conventional therapies such as corticosteroid.

3.(ii).B.(2) Efficacy

3.(ii).B.(2).1) Japanese studies

Taking account of the disease conditions of intestinal-, neuro-, and vasculo-BD and the current treatment status, the applicant explained the study design in Japan as follows:

- Control group and target sample size

According to the number of medical care certificates issued for the patients with specified rare and intractable diseases in FY 2009, a total of 17,693 BD patients existed in Japan. Based on the report, patients with intestinal-, neuro-, and vasculo-BD account for 9.0%, 4.7%, and 2.4%, respectively, of all the BD patients in Japan (Kurosawa M et al., *Research on Behcet's disease supported by Health and Labour Sciences Research Grants [Research Project on Overcoming Intractable Disease]*, FY 2009 General Partial Research Report, 2010;60-65). The number of patients with intestinal-, neuro-, and vasculo-BD was estimated to be 1592, 832, and 425, respectively. However, the criteria set to include patients appropriate for the evaluation of the efficacy of infliximab and to exclude patients with high safety risk was considered to further limit the patients eligible for the clinical study, precluding a controlled clinical study with a large number of patients. Therefore, the applicant planned to conduct an open-label study in ≥3 patients for each disease type, 15 patients in total, for the sake of feasibility.

- Study patients

Since the clinical positioning is intended to be the treatment of patients with intestinal-, neuro-, and vasculo-BD who are unresponsive or intolerant to conventional therapies, the study patients were to be patients with intestinal-, neuro-, or vasculo-BD who had lesions despite treatment with conventional therapies or who could not receive conventional therapies because of intolerability.

- Efficacy endpoints and assessment duration

The symptoms and clinical courses of intestinal-, neuro-, and vasculo-BD widely vary among patients with each type of disease, and there is no clinically established efficacy endpoint for any disease type. Therefore, by taking account of the facts that patients with intestinal- and neuro (acute)-BD have exacerbations and remissions (Suzuki O, et al., *The Japanese journal of gastroenterological surgery*. 2002;35:1817-1820, Kikuchi H, et al., *Rheumatology*. 2008;40:519-525), that neuro (chronic progressive)-BD is a chronic progressive disease with poor prognosis (Kikuchi H, et al., *Riumachika (Rheumatology)*. 2008;40:519-525), and that target patients with vasculo-BD were those with vasculitis resistant to conventional therapies, efficacy was evaluated based on the combination of parameters used for efficacy evaluation in routine clinical practice, including clinical symptoms, morphological assessment (imaging findings), and inflammation markers such as blood test parameters over time, according to the characteristic features of each disease type. Marked improvement or suppression of progression, which is usually difficult to achieve if the treatment is not effective, was set as the criterion. Lasting marked improvement or suppression of progression for all of these endpoints was defined as a "complete response," and the percentage of patients with a "complete response" was defined as the primary efficacy endpoint of the study [see Table 2 in "3.(ii).A. Summary of the submitted data"].

The time point of the assessment of the primary endpoint was set at Week 30, by taking account of the following, together with the timing of the assessment of the treatment effect in published literature and in routine clinical practice: (i) Some patients with an inadequate response to conventional therapies have repeated relapses, and (ii) although there is only very limited information on the clinical course of patients with neuro (chronic progressive)- and vasculo-BD treated with infliximab, these are chronic progressive diseases.

- Dosage and administration

Remicade (infliximab) has been approved for the treatment of patients with refractory uveoretinitis associated with BD, with the dosage regimen of "5 mg/kg at Weeks 0, 2 and 6, and then every 8 weeks thereafter." In the Japanese and foreign clinical practice guidelines, administration of infliximab 5 mg/kg is recommended for patients with intestinal-, neuro-, and vasculo-BD. It is known that, with some of the diseases for which infliximab is indicated, the efficacy is attenuated in some patients when infliximab 5 mg/kg is administered every 8 weeks. In order to keep efficacy, it is considered critical to maintain the serum infliximab concentration at a certain level. Therefore, dose increase to 10 mg/kg and decreasing the dosing interval to 4 weeks have been approved for the treatment of RA, and dose increase to 10

mg/kg has been approved for Crohn's disease with attenuated response. Taking account of the above, the dosage regimen selected in this study was 5 mg/kg administered as intravenous infusion at Weeks 0, 2, and 6, and then every 8 weeks thereafter. Criteria for dose increase were set for patients with attenuated response to 5 mg/kg and, after the end of the assessment of the primary endpoint (at Week 30), infliximab at 10 mg/kg was allowed.

PMDA considers as follows:
Because of the extremely limited number of patients with intestinal-, neuro-, or vasculo-BD in Japan, it was inevitable to plan and conduct an open-label, uncontrolled study, with the target sample size determined from the feasibility point of view, and to have set the dosage regimen by referring to the approved indications, the Japanese and foreign clinical practice guidelines, and textbooks. Also, because of the absence of any established indices for clinical efficacy evaluation for intestinal-, neuro-, or vasculo-BD, it is understandable that efficacy endpoints had to be based on the combination of parameters used for efficacy evaluation in routine clinical practice, including specific clinical symptoms, morphological assessment (imaging findings), and inflammation markers such as blood test parameters over time, according to the characteristic features of each disease type.

3.(ii).B.(2).2) Efficacy in each disease type

(a) Efficacy in intestinal BD patients

The applicant explained the efficacy of infliximab for intestinal-BD patients as follows:
In the Japanese study (Study TA-650-23), the major results of the primary efficacy endpoint in intestinal-BD were as shown in Table 5. The number of patients with a complete response who showed disappearance of both clinical symptoms and imaging findings (endoscopy), the primary endpoint, was 6 of 11 patients at Week 14, 6 of 11 patients at Week 30, and 6 of 10 patients at Week 54. The percentage of patients rated as "0: no symptoms" increased over time up to Week 54, showing disappearance of symptoms such as abdominal pain, diarrhoea, and melaena. The primary ulcer was cured or scarred on imaging findings (endoscopy) in 9 of 11 patients at Week 14, and these improved conditions lasted up to Week 54. Inflammation markers remained at low levels up to Week 54. As regards dose reduction of, or weaning from, corticosteroid, 8 of 11 patients were using corticosteroid at the start of treatment (Week 0), but the dose was decreased in 3 of 8 patients at Week 14 (2 patients with complete response) and in 4 of 8 patients at Week 30 (3 patients with complete response), and 2 of them were weaned from corticosteroid (1 patient with complete response). At Week 54, the dose was reduced in 5 of 8 patients (3 patients with complete response), and 3 of them were weaned from corticosteroid (2 patients with complete response). All 4 patients who received a reduced dose or were weaned from corticosteroid at Week 30 continued to receive the reduced dose or were still weaned from corticosteroid up to Week 54 [Table 6].

Thus, in patients with intestinal-BD, administration of infliximab improved clinical symptoms and imaging findings (endoscopy), maintained the efficacy up to Week 54, and allowed a dose reduction of corticosteroid or weaning from corticosteroid.

Table 5. Results of main efficacy evaluation in intestinal-BD

Endpoint		Starting day of treatment (Week 0) (n = 11)	Week 2 (n = 11)	Week 14 (n = 11)	Week 30 (n = 11)	Week 54 (n = 10)
Number of patients with complete response		-	-	6	6	6
Clinical symptoms	Number of patients with improvement from baseline	-	7	8	10	8
	Number of patients rated as "0: no symptoms"	0	4	4	7	8
Imaging findings (endoscopy)	Longest diameter of the primary lesion (ulcer) (median [range]) (mm)	15 [1, 50]	-	0 [0, 25]	0 [0, 38]	0 [0, 20]
	Number of patients rated as "0: primary lesion (ulcer) cured or scarred"	-	-	9	9	8
Inflammation marker	CRP (median [range]) (mg/dL)	0.2 [0, 1.6]	0 [0, 0.5]	0.15 [0, 1.1]	0.10 [0, 3.5]	0.10 [0, 10.2]
Number of patients who underwent dose reduction of corticosteroid (n = 8)		-	-	3	4	5

-: Not investigated

Table 6. Corticosteroid dose over time after the start of treatment with infliximab

Patient No.		Starting day of treatment (Week 0)	Week 14	Week 30	Week 54
Intestinal-BD	TA-650BD-[redacted]	10	10 (complete response)	7.5 (complete response)	5
	TA-650BD-[redacted]	10	5	10	10
	TA-650BD-[redacted]	7.5	7.5	7.5	7.5
	TA-650BD-[redacted]	15	7.5 (complete response)	0	0
	TA-650BD-[redacted]	2.5	2.5	0 (complete response)	0 (complete response)
	TA-650BD-[redacted]	12.5	12.5 (complete response)	12.5	12.5 (complete response)
	TA-650BD-[redacted]	3	3	3 (complete response)	0 (complete response)
	TA-650BD-[redacted]	20	15 (complete response)	10 (complete response)	10 (complete response)

Dose of corticosteroid (mg) (clinical effect)

PMDA considers as follows:
Given the limited number of the patients with intestinal-BD investigated in the Japanese study, there are limitations to evaluating the efficacy of infliximab based on the results of the study. However, clinical symptoms and imaging findings (endoscopy) improved in most of the enrolled patients at the assessment time points up to Week 54 and, in 6 of 11 patients, both clinical symptoms and imaging findings (endoscopy) disappeared and they were assessed as a "complete response" while usually patients with intestinal-BD have exacerbations and remissions. In addition, literature published in and out of Japan reported the infliximab -induced improvement in clinical symptoms, imaging findings, and laboratory data (e.g., CRP, ESR), as well as the dose reduction of corticosteroid, albeit based on data gathered in a retrospective manner. On the basis of these results and the descriptions in clinical practice guidelines and textbooks in and out of Japan, the efficacy of infliximab can be expected. Since only a limited number of patients were investigated in the clinical study, the efficacy of infliximab in patients with intestinal-BD should be further investigated in the post-marketing surveillance etc., after the market launch.

PMDA's conclusion on efficacy above will be discussed at the Expert Discussion.

(b) Efficacy in neuro-BD patients

The applicant explained the efficacy of infliximab in neuro-BD patients as follows:
The major results of efficacy evaluation in each of 3 patients with neuro-BD (2 acute neuro-BD patients, 1 chronic progressive neuro-BD patient) in the Japanese study (Study TA-650-23) were as shown in Table 7.

Of the 2 acute patients, 1 patient (Patient No. TA-650BD-[redacted]) experienced acute symptoms (pyrexia, headache), showed high intensity signal region on head MRI, increased cell count in spinal fluid (37/μL), and increased IL-6 concentration in spinal fluid (145 pg/mL) on the starting day of treatment (Week 0). By Week 2, acute symptoms disappeared, the high intensity signal region on head MRI shrank, and the

results of spinal fluid tests improved (cell count, 7/μL; IL-6 concentration, 1.8 pg/mL). At Week 22, a mild acute symptom (headache) was observed and the high intensity signal region did not disappear on head MRI. Because of these results, the patient was not rated as a "complete response" either at Weeks 14, 30, or 54. However, at Weeks 14, 30, and 54, the patient did not have any acute symptom, showed shrinkage of the high intensity signal region on head MRI, and had decreases in cell count and IL-6 concentration on spinal fluid test. In addition, the dose of corticosteroid was reduced with the improvement in symptoms.

The other acute patient (patient No. TA-650BD-[redacted]) did not show acute symptoms on the first day of treatment (Week 0) but experienced headache as a chronic symptom and showed high intensity signal region in the right frontal and parietal lobes on head MRI. Cell count and IL-6 concentration in spinal fluid were normal. After the assessment at 22 weeks after the start of treatment, the study was discontinued upon the request of the patient. IL-6 concentration increased at Week 14 and, for this reason, the patient was not rated as a "complete response" either at Week 14 or at the study discontinuation. As regards imaging findings, no new high intensity signal region was detected on head MRI at Week 14 or at the study discontinuation, while there was no change in the range of high intensity signal in the right frontal and parietal lobes on head. As regards clinical symptoms, no new acute symptoms occurred from the first dose until study discontinuation, whereas chronic headache persisted. Cell count in spinal fluid was low, and the dose of corticosteroid was reduced with the improvement in symptoms.

The chronic progressive neuro-BD patient (patient No. TA-650BD-[redacted]) showed slightly slow response as a clinical symptom on the first day of treatment (Week 0), and increased IL-6 concentration in spinal fluid (64.5 pg/mL), while no abnormal findings were detected on head MRI. The slowness of response disappeared at Week 6 and, from Week 14 onward, the patient remained asymptomatic. IL-6 concentration in spinal fluid increased to 430.0 pg/mL at Week 2, but decreased to 35.1, 5.4, and 32.1 pg/mL at Weeks 14, 30, and 54, respectively, below the level at baseline (Week 0). No shrinkage of the brain stem area was observed on head MRI up to Week 54, and the patient was rated as a "complete response" at Weeks 14, 30, and 54. The dose of corticosteroid remained unchanged at 18 mg/day.

Thus, among neuro-BD patients, only 1 chronic progressive neuro-BD patient had a complete response, but clinical symptoms improved without any aggravation of imaging findings in acute or chronic progressive neuro-BD patients. Decreases in cell count and IL-6 concentration in spinal fluid were observed, and the dose of corticosteroid was reduced in 2 of 3 patients.

Table 7. Results of main efficacy assessment in neuro-BD patients

Patient No.	Endpoint	Starting day of treatment (Week 0) (n = 3)	Week 2 (n = 3)	Week 14 (n = 3)	Week 30 (n = 2)	Week 54 (n = 2)	At discontinuation
Number of patients with complete response		-	-	1	1	1	-
Neuro-BD (acute)							
TA-650BD-[redacted]	Clinical symptoms	Pyrexia, headache	No symptoms	No symptoms	No symptoms	No symptoms	
	Imaging findings (head MRI)	High intensity signal region	High intensity signal region shrank	High intensity signal region shrank	High intensity signal region shrank	High intensity signal region shrank	
	Cell count in spinal fluid (/μL)	37	7	4	1	≤1	
	IL-6 concentration in spinal fluid (pg/mL)	145	1.8	2.2	1.4	1.5	
	Frequency of attacks (times)	-	-	-	1	0	
	Dose of corticosteroid (mg)	10	10	10	7.5	7.5	
TA-650BD-[redacted]	Clinical symptoms	Chronic headache	No symptoms	Improved			No symptoms
	Imaging findings (head MRI)	High intensity signal region	-	High intensity signal region shrank			High intensity signal region shrank
	Cell count in spinal fluid (mm^3)	3	-	2			2
	IL-6 concentration in spinal fluid (pg/mL)	2.5	-	23			6.5
	Frequency of attacks (times)	-	-	-			0
	Dose of corticosteroid (mg)	22.5	22.5	15			13
Neuro-BD (chronic progressive)							
TA-650BD-[redacted]	Clinical symptoms	Slight slowness in response	Unchanged	No symptoms	No symptoms	No symptoms	
	Imaging findings (head MRI)	-	-	Brainstem area unchanged	Brainstem area unchanged	Brainstem area unchanged	
	IL-6 concentration in spinal fluid (pg/mL)	64.5	430.0	35.1	5.4	32.1	
	Dose of corticosteroid (mg)	18	18	18	18	18	

PMDA considers as follows:
Given the limited number of patients with neuro-BD investigated in the Japanese study, there are limitations to evaluating the efficacy of infliximab based on the results of this study. No acute neuro-BD patients were rated as a "complete response" at any assessment time point up to 52 weeks after the start of treatment, but showed an improving tendency in clinical symptoms and in imaging findings (head MRI), with cell count and IL-6 concentration in spinal fluid remaining at decreased levels. One patient with chronic progressive neuro-BD was rated as a "complete response." In addition, literature published in and out of Japan reported infliximab-induced improvement in clinical symptoms, improved or unchanged imaging findings, and decreased IL-6 concentration in spinal fluid, as well as the dose reduction of corticosteroid, albeit based on data gathered in a retrospective manner. On the basis of these results and the descriptions in clinical practice guidelines and textbooks in and out of Japan, the efficacy of infliximab can be expected in both acute and chronic progressive neuro-BD patients. Since only a limited number of patients were investigated in the clinical study, the efficacy of infliximab in patients with neuro-BD should be further investigated in the post-marketing surveillance etc., after the market launch.

PMDA's conclusion on efficacy above will be discussed at the Expert Discussion.

(c) Efficacy in vasculo-BD patients

The applicant explained the efficacy of infliximab in vasculo-BD patients as follows:

The major results of efficacy evaluation in patients with vasculo-BD[5] in the Japanese study (Study TA-650-23) were as shown in Table 8. Complete response was observed in 4 of 4 patients at Weeks 14, 30, and 54. Clinical symptoms were "asymptomatic" or "improved" in 3 of 4 patients at Weeks 2 and 14 and in 4 of 4 patients at Weeks 30 and 54, showing improvement in symptoms such as pain and swelling. Imaging findings (e.g., CT, PET/CT) were rated as "improved" in 3 of 4 patients at Weeks 14, 30, and 54, with shrinkage of thrombus observed on CT and disappearance of abnormal findings on PET/CT. In 1 of 4 patients, venous thrombus was detected at baseline, which disappeared on an imaging test at Week 2, and did not occur again up to Week 54. In 3 of 4 patients, no venous thrombus was observed during the study period. As regards inflammation markers, both CRP and ESR decreased at Week 2, and remained at decreased levels up to Week 54. As for dose reduction of or weaning from, corticosteroid, among 3 patients who were using corticosteroid at the first day of treatment (Week 0), 2 patients (both with complete response) had a dose reduction at Weeks 14 and 30, and all 3 patients (all with complete response) at Week 54. In both patients receiving the reduced dose at Week 30, the reduced dose was maintained up to Week 54.

Thus, in patients with vasculo-BD, administration of infliximab resulted in improvement of clinical symptoms, imaging findings, and inflammation marker levels, as well as a long-lasting effect up to Week 54 and the dose reduction of corticosteroid [Table 9].

Table 8. Results of main efficacy assessment in vasculo-BD patients

Endpoint		Starting day of treatment (Week 0) (n = 4)	Week 2 (n = 4)	Week 14 (n = 4)	Week 30 (n = 4)	Week 54 (n = 4)
Number of patients with complete response		-	-	4	4	4
Clinical symptoms	Number of patients rated as "0: asymptomatic"	-	1	1	0	0
	Number of patients rated as "1: improved"	-	2	2	4	4
	Number of patients rated as "2: unchanged"	-	1	1	0	0
Imaging findings (CT, PET/CT)	Number of patients rated as "0: improved"	-	-	3	3	3
	Number of patients rated as "1: unchanged"	-	-	1	1	1
Inflammation markers	CRP (median [range]) (mg/dL)	0.9 [0.3, 4.3]	0.25 [0, 0.4]	0.15 [0.1, 0.4]	0.10 [0, 0.2]	0.15 [0, 0.2]
	Change from starting day of treatment (median) (mg/dL)	-	-0.60	-0.60	-0.75	-0.85
	ESR (median [range]) (mm/hr)	31.0 [16, 36]	11.0 [4, 17]	8.5 [3, 13]	4.5 [4, 14]	6.5 [2, 9]
	Change from starting day of treatment (median) (mm/hr)	-	-18.0	-18.5	-22.5	-22.5
Number of patients without venous thrombosis from starting day of treatment to assessment time point		-	-	-	4	4
Number of patients who underwent dose reduction of corticosteroid (n = 3)		-	0	2	2	3

-: Not investigated

Table 9. Corticosteroid dose over time from the start of treatment with infliximab

Patient No.		Starting day of treatment (Week 0)	Week 14	Week 30	Week 54
Vasculo-BD	TA-650BD-[redacted]	13	10 (complete response)	9 (complete response)	7.5 (complete response)
	TA-650BD-[redacted]	10	10 (complete response)	10 (complete response)	9 (complete response)
	TA-650BD-[redacted]	5	2.5 (complete response)	2.5 (complete response)	2.5 (complete response)

Dose of corticosteroid (mg) (clinical efficacy)

PMDA considers as follows:
Given the limited number of the patients with vasculo-BD investigated in the Japanese study, there are limitations to evaluating the efficacy of infliximab based on the results of the study. However, all 4 patients enrolled, including patients resistant or refractory to corticosteroid and other conventional therapies, were rated as a "complete response" up to Week 54. In addition, literature published in and out of Japan reported infliximab-induced improvement of clinical symptoms, imaging findings, and laboratory data (e.g., CRP, ESR), as well as dose reduction of corticosteroid, albeit based on data gathered in a retrospective manner. On the basis of these results and the descriptions in clinical practice guidelines and textbooks in and out of Japan, the efficacy of infliximab can be expected. Since only a limited number of patients were investigated in the clinical study, the efficacy of infliximab in patients with vasculo-BD should be further investigated in the post-marketing surveillance etc., after the market launch.

PMDA's conclusion on efficacy above will be discussed at the Expert Discussion.

3.(ii).B.(3) Safety
The applicant explained the safety of infliximab in patients with intestinal-, neuro-, or vasculo-BD, as follows:
The incidences of adverse events by disease type in the Japanese study were as shown in Table 10. No significant difference was observed in the occurrences of adverse events among the 3 disease types. Serious adverse events were observed only in patients with intestinal-BD (11.1% [2 of 18 patients]). They were cataract and Behcet's syndrome in 1 patient each, which were aggravation of the complication and of the primary disease, respectively, and their causal relationship to infliximab was ruled out. The incidence of infection was 63.6% (7 of 11 patients) in patients with intestinal-BD, 33.3% (1 of 3 patients) in patients with neuro-BD, and 75.0% (3 of 4 patients) in patients with vasculo-BD. Infusion reaction[6] was observed only in 1 patient with intestinal-BD (mild headache). Among infliximab-induced clinically significant events to which the package insert calls for attention, tuberculosis, malignant tumour, autoimmune disease (lupus-like symptom), delayed hypersensitivity reaction, demyelinating disease, and rhabdomyolysis were not observed in the Japanese study.

Table 10. Incidences of adverse events in patients with intestinal-, neuro-, or vasculo-BD in the Japanese study

	3 disease types combined (n = 18)	Intestinal-BD (n = 11)	Neuro-BD (n = 3)	Vasculo-BD (n = 4)
Adverse events	17 (94.4)	10 (90.9)	3 (100.0)	4 (100.0)
Adverse drug reactions	12 (66.7)	8 (72.7)	1 (33.3)	3 (75.0)
Serious adverse events	2 (11.1)	2 (18.2)	0	0
Adverse events leading to study discontinuation	0	0	0	0
Infection	11 (61.1)	7 (63.6)	1 (33.3)	3 (75.0)
Serious infection	0	0	0	0
Infusion reaction	1 (5.6)	1 (9.1)	0	0
Serious infusion reaction	0	0	0	0

Number of patients (%)

Safety data were compared among 3 disease types of BD combined, BD (uveoretinitis) in the Japanese clinical study, approved indications, and all diseases combined [Table 11]. The incidences of adverse events, adverse drug reactions, or serious adverse events in patients with BD (3 disease types combined) tended not to be higher compared with those in patients with BD (uveoretinitis), in patients with approved indications, or in all patients combined. There were no events that occurred in ≥2 patients with BD (3 disease types combined) but in no patients with other diseases. Except for Behcet's syndrome, no serious events occurred. The incidences of infection and infusion reaction in patients with BD (3 disease types combined) did not exceed those in patients with BD (uveoretinitis), in patients with approved indications, or in patients with all diseases combined. As regards the occurrences of anti-double stranded (ds) DNA antibodies in Japanese study, the incidence of increase in antinuclear antibody was 11.1% (2 of 18 patients) in patients with BD (3 disease types), 32.0% (8 of 25 patients) in patients with BD

[6] Infusion reaction was defined as an adverse event that occurred during or within 2 hours after the administration of infliximab.

(uveoretinitis), and 16.1% (165 of 1022 patients) in patients with all diseases combined. The incidence of increase in anti-dsDNA antibody (IgM) was 44.4% (8 of 18 patients) in patients with BD (3 disease types), 72.0% (18 of 25 patients) in patients with BD (uveoretinitis), and 56.3% (575 of 1022 patients) in patients with all diseases combined. Increase in anti-dsDNA antibody (IgG) was not observed either in patients with BD (3 disease types) or in patients with BD (uveoretinitis), but observed in 2.6% (27 of 1022 patients) of patients with all diseases combined. These results suggested that the infliximab-induced risk of increase in antinuclear antibody, anti-dsDNA antibody (IgM), or anti-dsDNA antibody (IgG) in patients with intestinal-, neuro-, or vasculo-BD was not significantly different compared with the risk in patients with approved indications.

The above results, taken together, suggest that there is no significant difference in the tendency of the occurrences of adverse events among patients with intestinal-, neuro-, and vasculo-BD, and that the safety profile in patients with intestinal-, neuro-, or vasculo-BD receiving infliximab is not significantly different from that in patients treated with infliximab for approved indications. However, since only a limited number of patients were investigated in the Japanese study and it cannot be ruled out that serious adverse events observed in patients with approved indications may occur also in patients with intestinal-, neuro-, or vasculo-BD, precautions should be provided to these serious adverse events as is the case with approved indications.

Table 11. Incidences of adverse events following the administration of infliximab in Japanese clinical studies

	BD (3 disease types combined) (n = 18)	BD (uveoretinitis) (n = 25)	RA (n = 561)	Crohn's disease (n = 167)	Ulcerative colitis (n = 104)	Inflammatory bowel disease (n = 271)	Psoriasis (n = 114)	Ankylosing spondylitis (n = 33)	All diseases combined (n = 1022)
Adverse events	17 (94.4)	25 (100)	543 (96.8)	155 (92.8)	100 (96.2)	255 (94.1)	110 (96.5)	33 (100)	983 (96.2)
Adverse drug reactions	12 (66.7)	25 (100)	500 (89.1)	138 (82.6)	76 (73.1)	214 (79.0)	108 (94.7)	30 (90.9)	889 (87.0)
Serious adverse events	2 (11.1)	5 (20.0)	65 (11.6)	38 (22.8)	18 (17.3)	56 (20.7)	12 (10.5)	4 (12.1)	144 (14.1)
Adverse events leading to study discontinuation	0	5 (20.0)	76 (13.5)	28 (16.8)	7 (6.7)	35 (12.9)	15 (13.2)	2 (6.1)	133 (13.0)
Infection	11 (61.1)	20 (80.0)	341 (60.8)	117 (70.1)	62 (59.6)	179 (66.1)	88 (77.2)	26 (78.8)	665 (65.1)
Serious infection	0	1 (4.0)	32 (5.7)	18 (10.8)	1 (1.0)	19 (7.0)	2 (1.8)	0	54 (5.3)
Infusion reaction	1 (5.6)	18 (72.0)	188 (33.5)	46 (27.5)	16 (15.4)	62 (22.9)	21 (18.4)	7 (21.2)	297 (29.1)
Serious infusion reaction	0	0	2 (0.4)	1 (0.6)	0	1 (0.4)	1 (0.9)	0	4 (0.4)

Number of patients (%)

PMDA concluded that neither the frequency of adverse events nor the safety profile of infliximab in patients with intestinal-, neuro-, or vasculo-BD is particularly different from those in patients with BD (uveoretinitis) or in patients with approved indications based on the case reports from the Japanese study and published literature. However, given the extremely limited number of patients investigated in the Japanese study, it is necessary to pay attention to known adverse drug reactions and to closely monitor the conditions of the patient for possible adverse events specific to intestinal-, neuro-, or vasculo-BD. The safety of infliximab in patients with intestinal-, neuro-, and vasculo-BD should continue to be investigated in the post-marketing surveillance.

3.(ii).B.(4) Indications

Based on the data submitted by the applicant and on the descriptions in the latest clinical practice guidelines and textbooks in and out of Japan, PMDA confirmed that the efficacy of infliximab, alone or in combination with MTX, has been demonstrated and that the drug can be a treatment option for patients who had an inadequate response to conventional therapies such as corticosteroid, both in and out of Japan [see “3.(ii).B.(1) Clinical positioning”]. PMDA also concluded that it is acceptable to set the indication as “The following diseases which are refractory to conventional therapies: intestinal-Behcet's disease, neuro-Behcet's disease, vasculo-Behcet's disease” in line with the applicant’s proposal, based on the review in “3.(ii).B.(2) Efficacy” and “3.(ii).B.(3) Safety.”

3.(ii).B.(5) Dosage and administration

PMDA considers that it is acceptable to set the dosage regimen of Remicade (infliximab) for patients with intestinal-, neuro-, or vasculo-BD as "5 mg/kg of Infliximab (Genetical Recombination) at Weeks 0, 2, and 6, and then every 8 weeks thereafter," based on the review in "3.(ii).B.(2) Efficacy" and "3.(ii).B.(3) Safety" as well as on the descriptions in clinical practice guidelines and textbooks in and out of Japan.

In the Japanese study (Study TA-650-23), the dose of infliximab was increased to 10 mg/kg only in 3 patients with intestinal-BD, and none of them were rated as a "complete response" after the dose increase. PMDA asked the applicant to explain whether or not the dose increase to 10 mg/kg is necessary in patients with intestinal-, neuro-, or vasculo-BD.

The applicant explained as follows:

In the Japanese study, the dose of infliximab was to be increased to 10 mg/kg every 8 weeks if response was attenuated after the end of the primary endpoint assessment (Week 30). In 3 patients with intestinal-BD who showed clinical symptoms such as abdominal pain or increased ulcer diameter on endoscopy, the dose was increased to 10 mg/kg (1 patient each at Weeks 30, 38, and 46). The results of the main efficacy assessments before and after dose increase in these patients were as shown in Table 12. After the dose increase, clinical symptoms did not disappear in any of the 3 patients, precluding rating them as a "complete response," but the clinical symptoms tended to improve and CRP decreased. Serum infliximab concentration increased after dose increase [see "3.(i) Summary of biopharmaceutic studies and clinical pharmacology studies"].

As regards the safety of the dose increase, an adverse event (Behcet's syndrome) was observed in 1 of 3 patients after the dose increase to 10 mg/kg. This patient was hospitalized at Week 54 because of the aggravation of intestinal-BD. The adverse event was assessed as serious, but its causal relationship to infliximab was ruled out since it was associated with the aggravation of the primary disease. The dose of infliximab was increased to 10 mg/kg in only a few patients with intestinal-, neuro-, or vasculo-BD. However, the safety profile of infliximab administered at 10 mg/kg to patients with RA or Crohn's disease is already known, and it has been shown that the risk of adverse events does not increase after dose increase. Therefore, provided that 5 mg/kg is well tolerated, it is considered possible to control the safety risk of infliximab by paying attention to known risks even with the dose increase from 5 mg/kg to 10 mg/kg.

In the Japanese study, a limited number of patients were investigated and only a few of them required dose increase. In contrast, with approved indications such as RA and Crohn's disease, it is known that the effective serum infliximab concentration cannot be maintained in some patients for 8 weeks even if they are treated with the recommended dosage, resulting in inadequate or attenuated response. Also, in patients with RA, the relationship between serum infliximab concentration and the efficacy is suggested. Therefore, it has been approved to increase the dose up to 10 mg/kg or to decrease the dosing interval to 4 weeks (*Review Report on "Remicade for I.V. Infusion 100,"* 2009). Furthermore, published literature reported that, in patients with intestinal-, neuro-, or vasculo-BD, the efficacy of infliximab was maintained by dose increase to >5 mg/kg or by decreasing the dosing interval (Kinoshita H, et al., *Intern Med.* 2013;52:1855-1862, Li J, et al., *Intern Med J.* 2014;44:96-100, Adler S, et al., *Arthritis Care Res*. 2012;64:607-611, Ishige T, et al., *Research on Behcet's disease supported by Health and Labour Sciences Research Grants [Research Project on Overcoming Intractable Disease], FY 2011 General Partial Research Report*. 2012;128). The above observations suggest that, as is the case with approved indications, among patients with intestinal-, neuro-, or vasculo-BD for which involvement of TNF is implicated, there are some patients in whom dose increase to 10 mg/kg is required and expected to be effective. Intestinal-, neuro-, and vasculo-BD seriously affect patients' life and there are no alternative choices available for patents who had an inadequate response to conventional therapies. Therefore, for patients with inadequate or attenuated response to 5 mg/kg, the dose increase of Remicade (infliximab) to 10 mg/kg can be a useful treatment option.

Table 12. Results of main efficacy assessments before and after dose increase in the Japanese study (3 patients with intestinal-BD)

Patient No.	Endpoint	At the starting day of treatment	At the time point of main efficacy assessment	At dose increase	4 weeks after dose increase	8 weeks after dose increase	12 weeks after dose increase	16 weeks after dose increase	At discontinuation
TA-650BD-[redacted]	Dosing period	Week 0	Week 30	Week 46	Week 50	Week 54			
	Clinical symptoms (details)	Slightly bad (occasional mild abdominal pain)	No symptoms	Somewhat bad (abdominal pain slightly interfering with activities of daily living)	Slightly bad (abdominal pain scarcely interfering with activities of daily living)	Slightly bad (abdominal pain improved from the last assessment)			
	Longest diameter of the primary lesion (ulcer) (mm)	14	0	-	-	0			
	CRP (mg/dL)	0.4	0.0	0.0	0.1	0.0			
	Dose of corticosteroid (mg)	10	7.5	5	5	5			
TA-650BD-[redacted]	Dosing period	Week 0	Week 30	Week 38	Week 42	Week 46	Week 50	Week 54	
	Clinical symptoms (details)	Slightly bad (watery stool after every meal and mild abdominal pain)	Slightly bad (mild abdominal pain persisting every day)	Bad (moderate abdominal pain almost every day, melaena, diarrhoea, and pyrexia)	Slightly bad (abdominal pain improved to mild. Diarrhoea. Melaena disappeared and pyrexia improved to mild)	Somewhat bad (abdominal pain, watery stool 6 times a day)	Slightly bad (abdominal pain, mushy stool 4 times a day)	Very bad (severe abdominal pain)	
	Longest diameter of the primary lesion (ulcer) (mm)	10	0	-	-	-	-	-	
	CRP (mg/dL)	0.0	2.2	11.7	1.2	4.2	3.1	10.2	
	Dose of corticosteroid (mg)	10	10	10	10	10	10	10	
TA-650BD-[redacted]	Dosing period	Week 0	Week 30	Week 30	Week 34	Week 38			
	Clinical symptoms (details)	Somewhat bad (abdominal pain)	Slightly bad (piercing abdominal pain)	Same as left	Slightly bad (very mild abdominal pain)	Slightly bad (severe abdominal pain with pyrexia)			Bad (abdominal pain, pyrexia, severe general malaise)
	Longest diameter of the primary lesion (ulcer) (mm)	13	38	Same as left	-	-			60
	CRP (mg/dL)	0.0	3.5	Same as left	0.0	4.6			6.1
	Dose of corticosteroid (mg)	-	-	Same as left	-	-			-

-: Not applicable

PMDA considers as follows:

In the Japanese study, dose increase was required only in a small number of patients, and did not result in a "complete response" after dose increase in any of them. However, a temporary improvement in clinical symptoms and decreased CRP level were observed after dose increase in some patients. Also, no safety concerns are suggested. In addition, there are case reports of the maintenance of the drug effect by dose increase to >5 mg/kg or by decreasing the dosing interval. Taking account of the above observations and the fact that, in patients with intestinal-, neuro-, or vasculo-BD who have an inadequate response to conventional therapies, there are only extremely limited treatment options, it is acceptable

to increase the dose of Remicade (infliximab) to 10 mg/kg if a patient has an inadequate or attenuated response to the 5 mg/kg dose. However, as is the case with approved indications, it is necessary to provide a caution not to unnecessarily continue the administration of Remicade without careful consideration if no improvement is achieved or aggravation of symptoms is evident after dose increase.

PMDA's conclusion on the dosage regimen above will be discussed at the Expert Discussion.

3.(ii).B.(6) Post-marketing safety measures

PMDA asked the applicant to explain the post-marketing safety measures in patients with intestinal-, neuro-, or vasculo-BD.

The applicant explained as follows:

Patients with BD mainly consult internal medicine specialists, dermatologists, or ophthalmologists, and are treated through cooperation among these specialists. The research on Behcet's disease (Inaba H, *FY 2003 General Partial Research Report, supported by Health and Labour Sciences Research Grants [Research Project on Overcoming Intractable Disease]*. 2004;95-113) states that many patients tend to visit relatively large medical institutions with multiple medical departments where interdepartmental collaboration is being sought. Also, it is expected that most physicians who use Remicade (infliximab) to treat intestinal-, neuro-, or vasculo-BD have already used Remicade for the treatment of approved indications including RA and Crohn's disease.

The same safety measures that have already been taken for approved indications will continuously be implemented even after approval of intestinal-, neuro-, and vasculo-BD to be added to the indications. For this purpose, the package insert will include precautionary statements that the use of conventional drugs should be considered for the treatment of intestinal-, neuro-, or vasculo-BD before administering Remicade, and that Remicade should be used by physicians with sufficient knowledge of Remicade and experience of treating intestinal-, neuro-, or vasculo-BD. Also, precautions will be provided that the medical institutions that use Remicade should (a) be equipped with appropriate drugs and therapeutic devices ready for use in case of emergency such as anaphylactic shock, and (b) be able to perform screening for respiratory infection including tuberculosis and to diagnose and treat adverse drug reactions such as tuberculosis, respiratory infection, and interstitial pneumonia, or otherwise, to coordinate with institutions capable of handling them.

In addition, in order to evaluate the long-term safety and efficacy of Remicade in the treatment of intestinal-, neuro-, and vasculo-BD in routine clinical practice, the applicant will conduct a specified use-results survey with the follow-up period of 1 year and target sample size of 110.

PMDA considers as follows:

The same safety measures as those taken in the treatment of approved indications should be taken in the treatment of intestinal-, neuro-, and vasculo-BD. Since only an extremely limited number of patients were investigated in the Japanese clinical study, the safety and efficacy of Remicade in patients with intestinal-, neuro-, and vasculo-BD in routine clinical practice should be investigated in the post-marketing surveillance, and information obtained should be provided to healthcare providers in clinical settings in an appropriate manner. Also, since dose increase to 10 mg/kg was performed in only a few patients in the Japanese clinical study, the safety and efficacy of Remicade in patients receiving the increased dose should continue to be investigated in the post-marketing surveillance.

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

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

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the partial change application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the partial change application (5.3.3.2.1, 5.3.5.2.1). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, a certain level of efficacy of Remicade (infliximab) in the treatment of patients with intestinal-, neuro-, and vasculo-BD who have an inadequate response to conventional therapies has been demonstrated and its safety is acceptable in view of its observed benefits. Remicade provides a new treatment option for patients with intestinal-, neuro-, and vasculo-BD who have an inadequate response to conventional therapies, and thus has clinical significance. As regards the safety, there is no evidence that suggests any significant difference in the safety profile of Remicade between patients with intestinal-, neuro-, or vasculo-BD and patients with approved indications. However, because the number of patients investigated in the clinical study was extremely limited, safety and efficacy in routine clinical practice should be further investigated in the post-marketing surveillance.

PMDA considered that Remicade may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

July 21, 2015

I. Product Submitted for Registration

[Brand name]	Remicade for I.V. Infusion 100
[Non-proprietary name]	Infliximab (Genetical Recombination)
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 30, 2014

II. Content of the Review

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

(1) Efficacy, indication, and dosage and administration

PMDA's conclusion on the efficacy, indication, dosage regimen of Remicade for I.V. Infusion 100 (hereinafter referred to as Remicade) as described in the Review Report (1) was supported by the expert advisors, with the following comments:

- There are limitations to the evaluation available from the results of the Japanese study (Study TA-650-23). However, because of the limited number of patients with intestinal-, neuro-, or vasculo-Behcet's disease (BD), it is acceptable that the study was conducted as an open-label, uncontrolled study.
- Given the results of the Japanese study and the descriptions in literature published in and out of Japan, Remicade is expected to be effective for the treatment of patients with intestinal-, neuro-, and vasculo-BD who had an inadequate response to conventional therapies.
- The results of the Japanese study (Study TA-650-23) suggested the effectiveness of increasing the dose of Remicade (infliximab) to 10 mg/kg. Based on these results and case reports in and out of Japan, it is considered possible to establish criteria for dose increase.

(2) Safety and risk management plan (draft)

PMDA's conclusion on the safety of Remicade as described in the Review Report (1) was supported by the expert advisors, with the following comments:

- Remicade may be used in combination with corticosteroid at a higher dose level than those for approved indications. Also, the possibility is pointed out that TNF inhibitors may induce and aggravate demyelinating neurological disease although the pathology is not the same as that of neuro-BD. Therefore, it is critical to provide precautions and take safety measures in treating intestinal-, neuro-, and vasculo-BD as in treating approved indications.
- Because the number of patients with intestinal-, neuro-, or vasculo-BD investigated in the Japanese study was limited, the safety profile in each disease type should continue to be investigated in the post-marketing surveillance.

Based on the review in "3.(ii).B.(3) Safety" and "2.(ii).B.(6) Post-marketing safety measures" of the Review Report (1) and on the comments raised by expert advisors at the Expert Discussions, PMDA concluded that the current risk management plan (draft) should include safety specifications and efficacy specifications as described in Table 13 and that pharmacovigilance activities and risk minimization actions should be conducted as shown in Table 14.

Table 13. Safety and efficacy specifications in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
- Serious infection - Tuberculosis - Delayed type hypersensitivity - Serious blood disorder - Lupus-like syndrome associated with positive anti-dsDNA antibody - Demyelinating disease - Hepatic impairment - Serious infusion reaction - Interstitial pneumonia - Rhabdomyolysis - Reactivation of hepatitis B - Antibody production	- Malignant tumour - Intestinal stenosis, intestinal obstruction (Crohn's disease, intestinal-BD)	- Safety in ankylosing spondylitis when administered every 8 weeks
Efficacy specifications		
- Efficacy in long-term use: effect on extraocular symptoms (refractory uveoretinitis caused by BD) - Efficacy when administered every 8 weeks: effect on extra-articular symptoms, imaging findings of sacroiliac joint and vertebral body (2 years) (ankylosing spondylitis) - Efficacy in long-term use (intestinal-, neuro-, and vasculo-BD)		

Table 14. Outline of additional pharmacovigilance activities and risk minimization actions in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization actions
- Use-results survey (all-case survey of refractory uveoretinitis caused by BD) - Specified use-results survey (all-case survey of ankylosing spondylitis) - Specified use-results survey (survey on the long-term use in the treatment of intestinal-, neuro-, and vasculo-BD)	- Preparation and provision of materials for healthcare professionals - Preparation and distribution of materials for patients - Secure provision of information on proper use of Remicade before product delivery

Based on the above, PMDA instructed the applicant to conduct a post-marketing surveillance to investigate these matters.

The applicant explained the plan to conduct a specified use-results survey with a 2-year follow-up period, involving a total of 150 patients with intestinal-, neuro-, and vasculo-BD who had an inadequate response to conventional therapies (≥25 patients for each disease type), as shown in Table 15, in order to investigate the safety and efficacy of Remicade in long term treatment in routine clinical practice, with serious infections (including tuberculosis, pneumocystis pneumonia, and cytomegalovirus infection), malignant tumour, infusion reaction, cytopenia, interstitial pneumonia, demyelinating disease, cardiac failure, and lupus-like syndrome being the priority investigation items, and to collect information on the safety and efficacy before and after increasing the dose of Remicade (infliximab) to 10 mg/kg.

Table 15. Outline of the plan for specified use-results survey (draft)

Objective	To investigate the safety and efficacy in the long-term use in routine clinical practice
Survey method	Central registration system
Patient population	Patients with intestinal-, neuro-, or vasculo-BD who had an inadequate response to conventional therapies
Observation period	2 years
Target sample size	150 patients (≥25 patients for each disease type)
Priority investigation items	Serious infections (including tuberculosis, pneumocystis pneumonia, and cytomegalovirus infection), malignant tumour, infusion reaction, cytopenia, interstitial pneumonia, demyelinating disease, cardiac failure, and lupus-like syndrome
Main investigation items	Patient characteristics (disease type of BD, disease duration, concurrent illness, past history, prior treatments, etc.) Concomitant drugs/therapies (use status, dose and treatment period, etc.) Use status of Remicade Efficacy evaluation Adverse events Laboratory test

PMDA considers that it is necessary to conduct the survey promptly and provide the collected information to healthcare providers in clinical settings in an appropriate manner.

III. Overall Evaluation

As a result of the above review, PMDA concludes that Remicade may be approved after modifying indication and dosage and administration as shown below, with the following conditions for approval. Remicade has been designated as an orphan drug for the indication of the present application. Therefore, the re-examination period should be 10 years.

[Indication]

Treatment of the following diseases in patients who had an inadequate response to conventional therapies:
- Rheumatoid arthritis (including prevention of structural damage to joint)
- Refractory uveoretinitis associated with Behcet's disease
- Plaque psoriasis, psoriatic arthritis, pustular psoriasis, erythrodermic psoriasis
- Ankylosing spondylitis
- <u>Intestinal-Behcet's disease, neuro-Behcet's disease, vasculo-Behcet's disease</u>

Treatment and maintenance therapy of Crohn's disease in the following patients (only in those who had an inadequate response to conventional therapies)
- Patients with moderately to severely active Crohn's disease or
- Patients with fistulizing Crohn's disease

Treatment of moderate to severe ulcerative colitis (only in patients who had an inadequate response to conventional therapies)

(Underline denotes added text.)

[Dosage and administration]

Rheumatoid arthritis

The usual dosage of infliximab is 3 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an inadequate or attenuated response at Week 6 or later, the dose may be increased or the dosing interval may be decreased in a stepwise manner. The dose may be increased up to 10 mg/kg at the dosing interval of 8 weeks and 6 mg/kg at a shorter dosing interval. The shortest dosing interval should be 4 weeks. Infliximab should be used in combination with methotrexate.

Refractory uveoretinitis associated Behcet's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Psoriasis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Ankylosing spondylitis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 6 to 8 weeks thereafter.

<u>Intestinal-Behcet's disease, neuro-Behcet's disease, vasculo-Behcet's disease</u>

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an inadequate or attenuated response at Week 6 or later, the dose may be increased to 10 mg/kg.

Crohn's disease

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter. If a patient has an attenuated response at Week 6 or later, the dose may be increased to 10 mg/kg.

Ulcerative colitis

The usual dosage of infliximab is 5 mg/kg administered as an intravenous infusion at Weeks 0, 2, and 6, then every 8 weeks thereafter.

Infliximab should be administered through an in-line filter with a microporous membrane of ≤1.2 μm.

(Underline denotes added text.)

[Conditions for approval] The applicant is required to develop a risk management plan and implement it appropriately.