Report on the Deliberation Results

September 14, 2016
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	(a) Humira 40 mg for S.C. Injection Syringe 0.8 mL
	(b) Humira 40 mg for S.C. Injection Syringe 0.4 mL
	(c) Humira 80 mg for S.C. Injection Syringe 0.8 mL
Non-proprietary Name	Adalimumab (Genetical Recombination) (JAN*)
Applicant	AbbVie GK
Date of Application	(a) October 29, 2015
	(b), (c) July 22, 2016

Results of Deliberation

In its meeting held on September 9, 2016, the Second Committee on New Drugs concluded that the partial change application 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 of the product is 4 years.

Conditions of Approval

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

** Japanese Accepted Name (modified INN)*

Review Report

August 30, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	(a) Humira 40 mg for S.C. Injection Syringe 0.8 mL (b) Humira 40 mg for S.C. Injection Syringe 0.4 mL (c) Humira 80 mg for S.C. Injection Syringe 0.8 mL
Non-proprietary Name	Adalimumab (Genetical Recombination)
Applicant	AbbVie GK
Date of Application	(a) October 29, 2015 (b), (c) July 22, 2016
Dosage Form/Strength	(a), (b) A solution for injection containing 40 mg of Adalimumab (Genetical Recombination) per syringe (c) A solution for injection containing 80 mg of Adalimumab (Ggenetical Recombination) per syringe
Application Classification	(a) Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage (b), (c) Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage, (10) Other drug[1)]
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis in patients who have had an inadequate response to conventional therapies and that the product has acceptable safety in view of its observed benefits (see Attachment).

As a result of its review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below, with the following conditions. Since serious adverse reactions to the product, such as infection, may occur, adequate advice is necessary to ensure that the product is used by physicians who are familiar with the treatment of non-infectious uveitis and have sufficient

1) Partial change application submitted to change the dosage and administration for Crohn's disease

knowledge of the product, in collaboration with physicians or other specialists who are experienced in monitoring and treating the adverse reactions. In addition, physicians should advised to observe the symptoms and conditions of patients thoroughly and then assess the risk and benefit of the product before making a treatment decision. The applicant should conduct a postmarketing surveillance study or other studies to monitor serious infection, malignant tumors or other events and should communicate new findings to physicians and patients appropriately.

Indication

Rheumatoid arthritis (including treatments to prevent structural damage in joints)

The following diseases in patients who have had an inadequate response to conventional therapies:

Psoriasis vulgaris and psoriatic arthritis

Ankylosing spondylitis

Active polyarticular juvenile idiopathic arthritis[2)]

Intestinal Behcet's disease

Non-infectious intermediate uveitis, posterior uveitis, or panuveitis

Remission induction and maintenance therapies for moderate to severe active Crohn's disease (only in patients who have had an inadequate response to conventional therapies)

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

(Underline denotes additions.)

Dosage and Administration

Rheumatoid arthritis

The usual adult dosage of Adalimumab (Genetical Recombination) is 40 mg administered once every 2 weeks by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Psoriasis vulgaris and psoriatic arthritis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 80 mg, followed by 40 mg once every 2 weeks. Adalimumab is administered by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Ankylosing spondylitis

The usual adult dosage of Adalimumab (Genetical Recombination) is 40 mg administered once every 2 weeks by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Active polyarticular juvenile idiopathic arthritis[2)]

The usual dosage of Adalimumab (Genetical Recombination) is as follows:

- patients weighing ≥15 kg and <30 kg: 20 mg once every 2 weeks
- patients weighing ≥30 kg: 40 mg once every 2 weeks

Adalimumab is administered by subcutaneous injection.

---

2) Indication or dosage and administration of Humira 40 mg for S.C. Injection Syringe 0.8 mL and Humira 40 mg for S. C. Injection Syringe 0.4 mL

Intestinal Behcet's disease

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

Non-infectious intermediate uveitis, posterior uveitis, or panuveitis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 80 mg, followed by 40 mg 1 week later, and then 40 mg once every 2 weeks starting 3 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

Crohn's disease

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection. If an decreased response is noted, the dose can be increased up to 80 mg per administration.[3)]

Ulcerative colitis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

(Underline denotes additions.)

Conditions of Approval

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

3) For Humira 40 mg for S.C. Injection Syringe 0.8 mL, a partial change application for a change to the dosage and administration for Crohn's disease was approved on June 20, 2016 (dotted underline denotes additions).

Attachment

Review Report (1)

July 19, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Humira 40 mg for S.C. Injection Syringe 0.8 mL
Non-proprietary Name	Adalimumab (Genetical Recombination)
Applicant	AbbVie GK
Date of Application	October 29, 2015
Dosage Form/Strength	A solution for injection containing 40 mg of Adalimumab (Genetical Recombination) per syringe

Proposed Indication

Rheumatoid arthritis (including treatments to prevent structural damage in joints)

The following diseases in patients who have had an inadequate response to conventional therapies:

Psoriasis vulgaris and psoriatic arthritis

Ankylosing spondylitis

Active polyarticular juvenile idiopathic arthritis

Intestinal Behcet's disease

Remission induction and maintenance therapies for moderate to severe active Crohn's disease (only in patients who have had an inadequate response to conventional therapies)

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

<u>Non-infectious intermediate uveitis, posterior uveitis, or panuveitis</u>

(Underline denotes additions.)

Proposed Dosage and Administration

Rheumatoid arthritis

The usual adult dosage of Adalimumab (Genetical Recombination) is 40 mg administered once every 2 weeks by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Psoriasis vulgaris and psoriatic arthritis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial

dose of 80 mg, followed by 40 mg once every 2 weeks. Adalimumab is administered by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Ankylosing spondylitis

The usual adult dosage of Adalimumab (Genetical Recombination) is 40 mg administered once every 2 weeks by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Active polyarticular juvenile idiopathic arthritis

The usual dosage of Adalimumab (Genetical Recombination) is as follows:

- patients weighing ≥15 kg and <30 kg: 20 mg once every 2 weeks
- patients weighing ≥30 kg: 40 mg once every 2 weeks

Adalimumab is administered by subcutaneous injection.

Intestinal Behcet's disease

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

Crohn's disease

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

Ulcerative colitis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

<u>Non-infectious uveitis</u>

<u>The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 80 mg, followed by 40 mg once every 2 weeks starting 1 week after the initial dose. Adalimumab is administered by subcutaneous injection.</u>

(Underline denotes additions.)

Table of Contents

List of Abbreviations

AAA	Anti adalimumab antibody
Adalimumab	Adalimumab (Genetical Recombination)
GCP	Good clinical practice
Humira	The commercial formulation
ITT	Intent-to-treat
NEI	National Eye Institute
PMDA	Pharmaceuticals and Medical Devices Agency
Steroid	Corticosteroid
SUN	Standardization of Uveitis Nomenclature
TNF-α	Tumor necrosis factor alpha

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The active ingredient of "Humira 40 mg for S.C. Injection Syringe 0.8 mL" is Adalimumab (Genetical Recombination). Adalimumab is a human immunoglobulin G (IgG) 1 monoclonal antibody specific for human tumor necrosis factor alpha (TNF-α) discovered by Knoll AG (current AbbVie Inc.). In Japan, the product was first approved for the indication of rheumatoid arthritis in April 2008, and subsequently it was approved for psoriasis vulgaris, Crohn's disease, ankylosing spondylitis, juvenile idiopathic arthritis and other diseases.

Uveitis is inflammation of the uvea (consisting of iris, ciliary body, and choroid), accompanied by visual impairment and eye pain, which may progress to blindness. On the basis of the criteria developed by the Standardization of Uveitis Nomenclature Working Group ("SUN") formed as part of the International Uveitis Study Group, uveitis is classified into anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis according to the main anatomical location of inflammation (*Am J Ophthalmol.* 2005;140:509-16). Patients with posterior uveitis or panuveitis are known to be at an

increased risk of visual impairment or blindness (*Arch Ophthalmol.* 2008;126:1191-201, *Br J Ophthalmol.* 1996;80:332-6). Uveitis is also classified according to whether it is caused by infection with bacteria or viruses (i.e., infectious or non-infectious uveitis). Non-infectious uveitis is further classified into the following disease types: sporadic eye syndrome such as birdshot chorioretinopathy; uveitis associated with systemic inflammation such as sarcoidosis, Vogt-Koyanagi-Harada disease, and Behcet's disease; and idiopathic uveitis which is not characterized by systemic lesions or clinical conditions suggestive of a specific disease (*Eur J Ophthalmol.* 2013;23:705-17, *Jpn J Ophthalmol.* 2012;56:432-5).

Currently, oral steroids are used as standard therapy for non-infectious intermediate uveitis, posterior uveitis, and panuveitis. However, some patients have an inadequate response to oral steroids while the use of oral steroid therapy may be restricted in other patients due to adverse reactions potentially resulting from its long-term use (e.g., progression of cataract, osteoporosis, abnormal glucose tolerance, weight gain) (*Am J Ophthalmol.* 2000;130:492-513). There is a need for new treatment options that can control inflammation in uveitis.

Additionally, immunosuppressive agents are used concomitantly with oral steroids in some cases, and cyclosporine is approved for the treatment of non-infectious uveitis in Japan. However, cyclosporine may cause adverse events such as renal impairment and hypertension. Infliximab (genetical recombination) is also approved for the treatment of refractory uveoretinitis associated with Behcet's disease in patients who have had an inadequate response to conventional therapies, but the drug has not been approved for the treatment of other forms of non-infectious uveitis. It may also raise the risk of serious infusion reaction and other adverse events.

In recent years, the literature has reported the involvement of an inflammatory cytokine TNF-α in the pathogenesis of non-infectious uveitis (*Br J Ophthalmol*. 2004;88:412-6). Adalimumab binds to human TNF-α with a high affinity, thereby inhibiting ligand-binding to the TNF receptor. For this reason, the applicant initiated the clinical development of adalimumab as a therapeutic agent for non-infectious intermediate uveitis, posterior uveitis, and panuveitis.

In Japan, the clinical development of adalimumab for the treatment of intermediate uveitis, posterior uveitis, and panuveitis started in August 2010. On the basis of the data from studies conducted in and outside of Japan, the applicant filed a partial change application for Humira (adalimumab). In the US and Europe, Humira was approved in June 2016 for the indication of non-infectious intermediate uveitis, posterior uveitis, and panuveitis.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application has been filed for approval of new indication and dosage and administration, no new data relating to quality has been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The effect of adalimumab in the animal model of uveitis was evaluated for the primary pharmacodynamic study.

3.l Effect of adalimumab in mouse model of uveitis (CTD 4.2.1.1)

B10.R III mice were immunized with interphotoreceptor retinoid-binding protein peptide and complete Freund's adjuvant to generate a mouse model of autoimmune uveoretinitis (*Meth Mol Med.* 2004;102:395-419). The mice were treated with anti-mouse TNF-α antibody (0.15-15 mg/kg), which is a murine surrogate for adalimumab, or anti-IgG antibody (negative control) once weekly (a total of 3 doses). The histological score of uveitis in autoimmune uveoretinitis mouse model tended to be lower in the animals treated with anti-mouse TNF-α antibody than in those treated with anti-IgG antibody (negative control).

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of adalimumab in patients with non-infectious uveitis:

Studies using animal models have reported that TNF-α, a pro-inflammatory cytokine produced mainly by macrophage or T-cells, plays an important role in the prolongation of inflammation in non-infectious uveitis by promoting leukocyte infiltration through adhesion molecule upregulation, macrophage activation, and dendritic cell maturation/survival (*Prog Retin Eye Res.* 2004;23:617-37). Also, the production of TNF-α was promoted by the expression of activated CD4-positive helper T cells in peripheral blood from patients with non-infectious uveitis, and the concentration of T cell-derived TNF-α was elevated in peripheral blood from patients with idiopathic intermediate uveitis or intermediate uveitis associated with sarcoidosis (*Br J Ophthalmol.* 2004;88:412-6). These clinical findings also suggest the involvement of TNF-α in the pathogenesis of non-infectious uveitis. On the basis of the above findings and the efficacy of anti-TNF-α antibody demonstrated in the autoimmune uveoretinitis mouse model, adalimumab is expected to be effective in patients with non-infectious uveitis.

PMDA accepted the above explanation of the applicant.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Since the present application has been filed for approval of new indication and dosage and administration, no new non-clinical pharmacokinetics data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application has been filed for approval of new indication and dosage and administration, no new toxicity study data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Biopharmaceutic studies and associated analytical methods

No new biopharmaceutic study data were submitted.

Serum adalimumab concentrations and anti-adalimumab antibody (AAA) were measured by enzyme-linked immunosorbent assay (lower limit of quantification [LLOQ] of serum adalimumab concentrations, 31.3 ng/mL; LLOQ of AAA, 10 ng/mL). The measured values below the LLOQ were regarded as 0 μg/mL.

6.2 Clinical pharmacology

The applicant submitted evaluation data including the results from the pharmacokinetic analysis of Study M10-877 and Study M10-880 (CTD 5.3.3.2-1, 5.3.3.2-2) conducted in patients with non-infectious uveitis and the population pharmacokinetic (PPK) analysis of these studies (CTD 5.3.3.5-1). Unless otherwise specified, pharmacokinetic parameters are shown in the form of mean ± SD.

6.2.1 Study M10-877 in patients with non-infectious uveitis (CTD 5.3.3.2-1)

A randomized, double-blind, placebo-controlled, parallel group study was conducted in patients with non-infectious uveitis (n = 118 in the adalimumab group). Adalimumab was administered at 80 mg (an initial loading dose) by subcutaneous injection, followed by 40 mg once every 2 weeks starting 1 week after the initial dose. Serum adalimumab concentrations were evaluated in the subjects treated. Table 1 shows the results.

AAA was detected in 4 subjects in the adalimumab group (including 1 Japanese patient).

Table 1. Serum adalimumab concentrations in patients with non-infectious uveitis in Study M10-877 (μg/mL)

	Week 1 (trough level)	Week 8	Week 12	Week 27 (trough level)	Week 36	Week 52
Japanese	7.1 ± 3.5 (n = 8)	4.4 ± 4.5 (n = 5)	6.5 ± 7.5 (n = 3)	-	-	-
Non-Japanese	7.9 ± 2.8 (n = 106)	8.6 ± 4.8 (n = 79)	9.2 ± 5.1 (n = 69)	9.5 ± 6.3 (n = 38)	9.5 ± 5.9 (n = 32)	10.0 ± 6.3 (n = 20)

Mean ± SD

6.2.2 Study M10-880 in patients with non-infectious uveitis (CTD 5.3.3.2-2)

A randomized, double-blind, placebo-controlled, parallel group study was conducted in patients with non-infectious uveitis (n = 131 in the adalimumab group). Adalimumab was administered at 80 mg (an initial loading dose) by subcutaneous injection, followed by 40 mg once every 2 week starting 1 week after the initial dose. Serum adalimumab concentrations were evaluated in the subjects treated. Table 2 shows the results.

AAA was detected in 8 patients in the adalimumab group (including 2 Japanese patients).

Table 2. Serum adalimumab concentrations in patients with non-infectious uveitis in Study M10-880 (μg/mL)

	Week 2	Week 8	Week 12	Week 27 (trough level)	Week 36	Week 52
Japanese	11.7 ± 3.9 (n = 16)	7.5 ± 5.9 (n = 13)	7.5 ± 4.9 (n = 7)	8.3 ± 6.3 (n = 7)	6.5 ± 5.8 (n = 5)	0, 9.2 (n = 2)
Non-Japanese	9.9 ± 3.7 (n = 114)	8.7 ± 5.1 (n = 100)	9.7 ± 5.4 (n = 90)	9.5 ± 7.1 (n = 63)	9.2 ± 5.6 (n = 54)	8.9 ± 5.2 (n = 41)

Mean ± SD

6.2.3 PPK analysis and exposure-response model analysis (CTD 5.3.3.5-1)

On the basis of serum adalimumab concentration data (1044 serum concentration samples from 248 patients) obtained in Phase III studies in patients with non-infectious uveitis (Studies M10-877 and M10-880), PPK analysis was performed by NONMEM (Version 7.3).

A 1-compartment model with the first-order absorption and the first-order elimination processes was developed as a basic model, and the final model included AAA, body weight, and concomitant drugs (concomitant methotrexate and concomitant mycophenolate mofetil) selected as covariates on CL/F (apparent clearance),[4)] and body weight as a covariate on for V_2/F (apparent volume of distribution for the central compartment). The PPK parameters, CL/F and V_2/F, estimated post hoc based on the final model (geometric mean [%CV]), were 14.98 mL/h (58.8%) and 8.00 L (21.4%), respectively. The estimated trough serum adalimumab concentrations (mean ± SD) at steady state in Japanese and non-Japanese patients were 6.63 ± 4.86 and 7.64 ± 4.31 μg/mL, respectively.

Adalimumab concentrations in individual patients were estimated by the PPK model. An exposure-response model was also developed based on the estimated adalimumab concentrations and the time to treatment failure in Phase III studies (Studies M10-877 and M10-880). Serum adalimumab concentrations required to reduce the time to treatment failure in the placebo group by 50% (IC_{50}) in Studies M10-877 and M10-880 was estimated to be 9.7 and 6.4 μg/mL, respectively.

6.R Outline of the review conducted by PMDA

PMDA's view:

Serum adalimumab concentrations in patients with uveitis did not tend to be higher than those in patients receiving multiple doses of adalimumab for the approved indications (see Table 3). From the perspective of clinical pharmacology, there were no new safety concerns in association with adalimumab used in patients with uveitis. The following points were also examined.

4) Factors examined as potential covariates on CL/F were age, gender, race, Japanese/non-Japanese, body weight, body surface area, lean body mass, height, AAA, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), total bilirubin, creatinine clearance, serum albumin, estimated creatinine clearance, alcohol consumption, smoking, disease characteristics, and concomitant drugs (prednisone, azathioprine, cyclosporine, methotrexate, mycophenolate mofetil). Factors examined as potential covariates on V_2/F were age, gender, race, Japanese/non-Japanese, body weight, body surface area, lean body mass, and height.

Table 3. Serum adalimumab concentrations after multiple doses of adalimumab by disease (Japanese subjects)

Disease	Uveitis		Crohn's disease	Ankylosing spondylitis	Ulcerative colitis	Intestinal Behcet's disease	Psoriasis
Study code	M10-877	M10-880	Japanese M06-837[a)]	Japanese M10-239	Japanese M10-447	Japanese M11-509	M04-688
Dosage and administration	Initial dose of 80 mg by subcutaneous injection (SC), followed by 40 mg once every 2 weeks starting 1 week after the initial dose		40 mg SC once every 2 weeks	40 mg SC once every 2 weeks	Initial dose of 160 mg SC, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks	Initial dose of 160 mg SC, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks	Initial dose of 80 mg SC, followed by 40 mg once every 2 weeks
Measuring point	Week 27 (trough level)		Week 24 (trough level)	Week 24 (trough level)	Week 32 (trough level)	Week 24 (trough level)	Week 24 (trough level)
Serum adalimumab concentration (μg/mL)	6.5 ± 7.5[b)] (n = 3)	8.3 ± 6.3 (n = 7)	6.8 ± 2.3 (n = 15)	8.4 ± 5.9 (n = 21)	8.7 ± 5.0 (n = 38)	9.1 ± 4.5 (n = 14)	3.8 ± 3.2 (n = 35)

Mean ± SD

a) An extension study of Study M04-729 in which adalimumab was administered at 160 mg (an initiale dose), followed by 80 mg 2 weeks later, or 80 mg (an initiale dose), followed by 40 mg 2 weeks later

b) Week 12

6.R.1 Ethnic difference in serum adalimumab concentration

The applicant considered that there were no clear, clinically relevant ethnic differences in serum adalimumab concentrations between Japanese and non-Japanese patients with uveitis, based on the following points.

- Serum adalimumab concentrations (mean ± SD [range]) in Japanese and non-Japanese patients with uveitis in pooled data from Phase III studies (Study M10-877 and Study M10-880) were 6.6 ± 5.6 [0, 19.0] μg/mL and 8.6 ± 4.9 [0, 25.0] μg/mL, respectively, at Week 8 and 8.3 ± 6.3 [0, 14.9] μg/mL and 9.5 ± 6.8 [0, 46.8] μg/mL, respectively, at Week 27 (trough level), showing a tendency toward slightly lower serum adalimumab concentrations in Japanese patients than in non-Japanese patients. However, these data do not necessarily demonstrate that this difference affect the efficacy of adalimumab in Japanese patients, because serum adalimumab concentrations in Japanese patients were within the range of serum adalimumab concentrations in subjects without treatment failure in Study M10-877 and Study M10-880 [see Section "6.R.2 Relationship between serum adalimumab concentrations and clinical response].

- In the PPK analysis, "Japanese" was not selected as a covariate on the pharmacokinetic parameters of adalimumab [see Section "6.2.3 PPK analysis and exposure-response model analysis (CTD 5.3.3.5-1)].

PMDA's view

The applicant's explanation is acceptable. There are no specific problems in the pharmacokinetic evaluation of data from the overall study population in Study M10-877 and Study M10-880.

6.R.2 Relationship between serum adalimumab concentrations and clinical response

The applicant's explanation about the relationship between serum adalimumab concentration and efficacy:

Table 4 shows serum adalimumab concentrations in subjects with or without treatment failure in Phase III studies (Studies M10-877 and M10-880). Treatment failure was defined as new onset of ocular inflammation or exacerbation of eye symptoms. Subgroup analysis showed a tendency toward slightly higher serum adalimumab concentrations in subjects without treatment failure than in subjects with treatment failure, but the range of serum adalimumab concentrations was similar between the two subgroups. Analysis of data by patient characteristics, including body weight, did not show a trend toward differences between subjects with and without treatment failure.

Moreover, the primary endpoint of these studies was time to treatment failure, defined as onset of ocular inflammation or exacerbation of eye symptoms. The exposure-response model analysis showed that the estimated serum adalimumab concentrations required to reduce the time to treatment failure in the placebo group by 50% (IC_{50}) was 9.7 μg/mL in Study M10-877 and 6.4 μg/mL in Study M10-880. This suggests that adalimumab concentrations cannot be maintained at the level that allows prevention of treatment failure.

Thus, reaching a definite conclusion regarding the relationship between serum adalimumab concentration and efficacy is considered difficult.

Table 4. Changes in serum adalimumab concentrations in subjects with or without treatment failure

		Week 1 or 2[a)]	Week 8	Week 12	Week 27 (trough level)	Week 36	Week 52
Study M10-877	Without treatment failure	7.7 ± 2.76 [2.5, 18.4] (n = 46)	9.0 ± 5.0 [0.6, 21.2] (n = 37)	10.2 ± 5.5 [0.05, 23.0] (n = 34)	10.8 ± 6.5 [0, 31.4] (n = 27)	9.9 ± 5.4 [1.1, 21.3] (n = 27)	10.0 ± 6.3 [0, 22.0] (n = 20)
	With treatment failure	7.9 ± 3.0 [1.5, 17.6] (n = 68)	7.8 ± 4.7 [0, 18.0] (n = 47)	8.1 ± 4.6 [0, 19.4] (n = 38)	6.1 ± 4.2 [0.5, 13.1] (n = 11)	7.2 ± 8.7 [0, 18.1] (n = 5)	—
Study M10-880	Without treatment failure	10.1 ± 3.9 [0.3, 21.0] (n = 73)	9.1 ± 4.8 [0, 25.0] (n = 67)	9.9 ± 5.1 [0.5, 22.4] (n = 65)	10.1 ± 7.2 [0, 46.8] (n = 55)	9.2 ± 5.6 [0, 28.8] (n = 51)	8.9 ± 5.2 [0, 27.1] (n = 42)
	With treatment failure	10.1 ± 3.7 [0.9, 17.7] (n = 57)	7.7 ± 5.6 [0, 21.6] (n = 46)	8.7 ± 5.8 [0, 23.9] (n = 32)	6.5 ± 5.8 [0, 19.5] (n = 15)	7.6 ± 6.4 [1.6, 20.5] (n = 8)	1.6 (n = 1)

Mean ± SD [range]; unit, μg/mL

a) The trough levels at Week 1 were evaluated in Study M10-877 and the serum adalimumab concentrations at Week 2 in Study M10-880.

PMDA asked the applicant to explain the clinical impact of the development of anti-adalimumab antibody (AAA).

The applicant's response:

Table 5 shows serum adalimumab concentrations by AAA status in Phase III studies (Studies M10-877 and M10-880). Although a definite conclusion on exposure-efficacy relationship cannot be reached due to a small number of subjects evaluated, serum adalimumab concentrations tended to be lower in AAA-positive patients than in AAA-negative patients. No marked difference in efficacy was noted between AAA-positive patients and AAA-negative patients. No particular safety concerns were noted in AAA-positive patients.

As described above, the use of adalimumab in patients with non-infectious uveitis suggested no particular clinically relevant effect associated with AAA development.

Table 5. Serum adalimumab concentration and time to treatment failure by AAA status

	Week 8	Week 12	Week 27 (trough level)	Week 36	Time to treatment failure[a)]
Study M10-877					
AAA positive	1.7 ± 3.4 (n = 4)	2.1 ± 4.1 (n = 4)	1.03, 1.62 (n = 2)	0 ± 0 (n = 2)	32 [16, 48]
AAA negative	8.7 ± 4.7 (n = 80)	9.5 ± 4.9 (n = 68)	9.9 ± 6.1 (n = 36)	10.1 ± 5.5 (n = 30)	15 [6, 52]
Study M10-880					
AAA positive	1.4 ± 2.4 (n = 7)	1.5 ± 2.4 (n = 6)	0 ± 0 (n = 3)	0, 0.43 (n = 2)	16 [10, 31]
AAA negative	9.0 ± 5.0 (n = 106)	10.1 ± 5.1 (n = 91)	9.8 ± 6.9 (n = 67)	9.3 ± 5.5 (n = 57)	16 [4, 60]

Mean ± SD; unit, μg/mL
a) Median [range]

PMDA's view:

The above analysis results and other data suggest the difficulty of reaching a definite conclusion on a relationship between the efficacy of adalimumab and serum adalimumab concentrations. Thus, the applicant's explanation is understandable. The clinical impact of AAA development is considered to be unknown at present. However, decreased serum adalimumab concentrations and reduced efficacy associated with the development of AAA were reported for the approved indications such as rheumatoid arthritis and psoriasis, and serum adalimumab concentrations tended to be lower in AAA-positive subjects with non-infectious uveitis than in AAA-negative subjects with non-infectious uveitis. In light of these findings, possible reduced efficacy of adalimumab in association with the development of AAA should continue to be investigated, based on the data from patients undergoing an AAA test, in the post-marketing surveillance study and other studies.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The results of Phase III studies (Studies M10-877 and M10-880) in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis were submitted for efficacy and safety evaluations.

7.1 Phase III study (CTD 5.3.5.1-1, Study M10-877 [August 2010 to August 2014])

A randomized, double-blind, placebo-controlled, parallel group study was conducted in 19 countries, including the US, Germany, and Japan, to evaluate the efficacy and safety of adalimumab in patients with active non-infectious intermediate uveitis, posterior uveitis, or panuveitis despite treatment with high-dose oral steroids[5)] (target sample size, 234 non-Japanese and 32 Japanese subjects).

Subjects were stratified by ethnicity (Japanese or non-Japanese). Non-Japanese subjects were stratified by use of baseline immunosuppressive therapy. A total of 239 patients were randomly allocated to the placebo group or adalimumab group (119 in the adalimumab group and 120 in the placebo group). All

5) Patients showing any of the following disease activity in either eye or both eyes at baseline, despite ≥2 weeks of treatment with a fixed dose of an oral steroid (≥10 to ≤60 mg prednisone or equivalent per day): (a) new active, inflammatory chorioretinal or retinal vascular lesions, (b) anterior chamber cell grade ≥2+ (SUN criteria), or (c) vitreous haze grade ≥2+ (National Eye Institute [NEI]/SUN criteria)

of the 239 subjects treated with study drug were included in the safety analysis population. Of the randomized subjects, 233 subjects (118 in the adalimumab group and 115 in the placebo group) were included in the intention-to-treat (ITT) population, and the remaining 6 subjects were excluded from analysis for reasons such as non-compliance with good clinical practice (GCP). The ITT population was used for the efficacy analysis. The study was discontinued in 15.3% (18 of 118) of subjects in the adalimumab group and 6.1% (7 of 115) of subjects in the placebo group. Main reasons for discontinuation included adverse events (8.5% [10 of 118] of subjects in the adalimumab group and 2.6% [3 of 115] of subjects in the placebo group). There was no discontinuation in the Japanese subgroup.

Subjects received an initial dose of 80 mg of adalimumab or placebo by subcutaneous injection, followed by 40 mg adalimumab or placebo once every 2 weeks starting 1 week after the initial dose for up to 80 weeks until the end of the study. In accordance with the protocol of this study, subjects were to receive a loading dose of prednisone for suppression of disease activity, and then were to undergo tapering of the dose.[6)]

The primary endpoint of the study was the time to treatment failure[7)] at or after Week 6 in the overall study population and the Japanese subgroup. Table 6 shows the results of the primary endpoint. Figures 1 and 2 show the Kaplan-Meier curves. The time to treatment failure at or after Week 6 in the overall adalimumab group was compared with that in the overall placebo group. The pairwise comparison exhibited statistically significant differences, demonstrating the superiority of adalimumab to placebo. Events occurring before Week 6 were not included in the tabulation because disease activity was controlled to normal levels after the loading dose of prednisone.

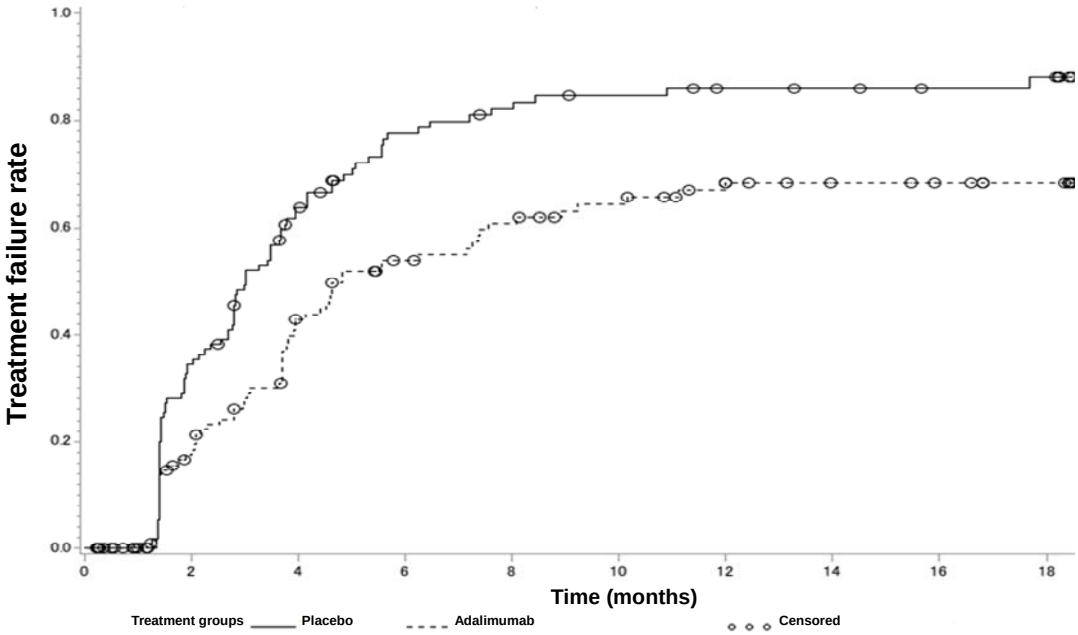
Table 6. Time to treatment failure at or after Week 6 (ITT population)

		Adalimumab	Placebo
Overall study population	Proportion of subjects who had treatment failure during the study period	57.6 (68/118)	78.3 (90/115)
	Median time to treatment failure (months)	4.8	3.0
	Hazard ratio [95% confidence interval (CT)][a)]	0.56 [0.40, 0.76]	
	P value[a)]	<0.001	
Japanese	Proportion of subjects who had treatment failure during the study period	100 (8/8)	75.0 (6/8)
	Median time to treatment failure (months)	2.4	2.8
	Hazard ratio [95% CI][b)]	1.20 [0.41, 3.54]	

% (n)
a) Cox proportional hazards model using treatment group and Japanese/non-Japanese as explanatory variables
b) Cox proportional hazards model using treatment group as an explanatory variable

6) Subjects were to receive prednisone 60 mg/day up to Week 2, and were to undergo a taper schedule, in which the daily dose was reduced by 10 mg weekly from Week 2 to Week 5, by 5 mg at Week 5, by 2.5 mg weekly from Week 6 to Week 10, by 1 mg weekly after Week 10. All subjects were off prednisone from Week 15 onward.

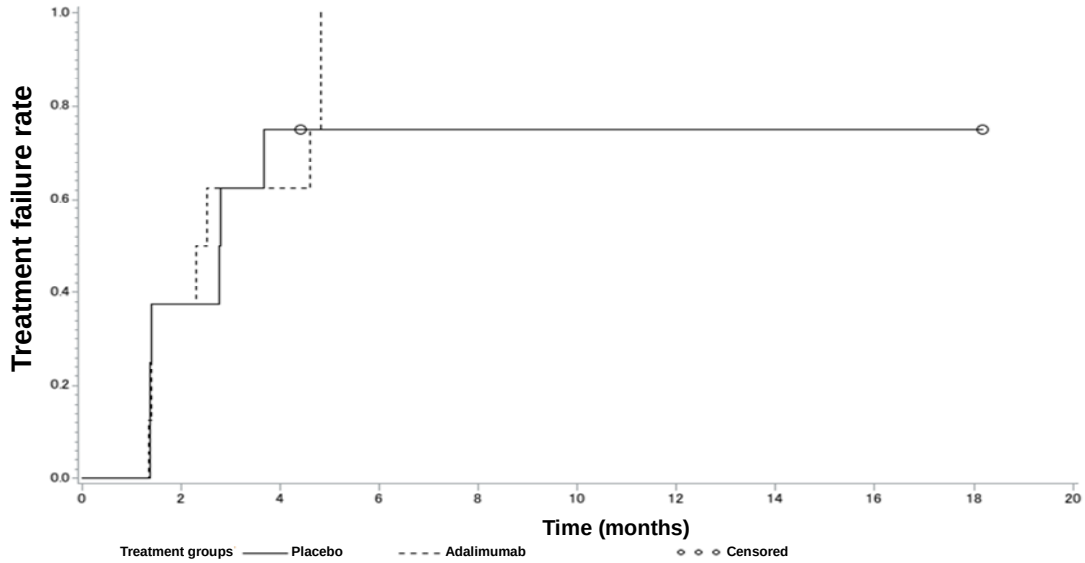
7) Treatment failure was defined as (a) new inflammatory chorioretinal lesions and/or retinal vascular lesions, (b) 2-step increase in anterior chamber cell grade (SUN criteria), (c) 2-step increase in vitreous haze grade (NEI/SUN criteria) or (d) worsening of best-corrected visual acuity by ≥15 letters).



Time (months)	0	2	4	6	8	10	12	14	16	18	20
Placebo	0/115	38/72	69/37	82/20	86/15	88/12	89/9	89/8	89/6	90/5	90/0
Adalimumab	0/118	19/87	45/57	56/42	62/35	65/29	68/20	68/17	68/15	68/12	68/0

(Cumulative number of subjects with treatment failure/number of subjects at risk)

Figure 1. Kaplan-Meier curve of treatment failure at or after Week 6 (overall study population, ITT population)



Time (months)	0	2	4	6	8	10	12	14	16	18	20
Placebo	0/8	3/5	6/2	6/1	6/1	6/1	6/1	6/1	6/1	6/1	6/0
Adalimumab	0/8	3/5	5/3	8/0	8/0	8/0	8/0	8/0	8/0	8/0	8/0

(Cumulative number of subjects with treatment failure/number of subjects at risk)

Figure 2. Kaplan-Meier curve of treatment failure at or after Week 6 (Japanese subgroup, ITT population)

Analysis of adverse events was performed for the overall population. Adverse events occurred in 84.9% (101 of 119) of subjects in the adalimumab group and 79.2% (95 of 120) of subjects in the

placebo group. Table 7 shows the major events. There was 1 death in the adalimumab group (chronic renal failure). A causal relationship between the event and the study drug was ruled out.

Serious adverse events occurred in 13.4% (16 of 119) of subjects in the adalimumab group (ureteral calculus, angle-closure glaucoma, anaphylactic reaction/urticaria, pilonidal cyst, pneumonia, tuberculosis, upper respiratory tract infection, urinary tract infection, accidental overdose, ligament rupture/tendon rupture, fluid overload/chronic renal failure, lupus-like syndrome, gastrointestinal carcinoid tumor, glioblastoma multiforme, demyelination, and angiogenesis in 1 subject each) and 5.0% (6 of 120) of subjects in the placebo group (acute hepatitis, primary hyperparathyroidism, viral gastroenteritis, acute pyelonephritis/sepsis, wrist fracture, and induced abortion in 1 subject each). Among them, adverse events for which a causal relationship to the study drug could not be ruled out by the investigator were lupus-like syndrome, demyelination, tuberculosis, pneumonia, upper respiratory tract infection, and glioblastoma multiforme in the adalimumab group and acute hepatitis and acute pyelonephritis/sepsis in the placebo group. Ureteral calculus, demyelination, tuberculosis, and glioblastoma multiforme remained unresolved.

Adverse events led to discontinuation in 9.2% (11 of 119) of subjects in the adalimumab group (choroidal neovascularization, blurred vision/ visual acuity reduced, fatigue/malaise, tuberculosis, increased value in light chain assay, Mycobacterium tuberculosis complex test positive, lupus-like syndrome, glioblastoma multiforme, demyelination, suicidal ideation, and chronic renal failure in 1 subject each) and 3.3% (4 of 120) of subjects in the placebo group (cystoid macular oedema/drug intolerance, eye deposit/vitreous detachment, and acute hepatitis in 1 subject each). Among them, adverse events for which a causal relationship to the study drug could not be ruled out were lupus-like syndrome, demyelination, tuberculosis, fatigue/malaise, Mycobacterium tuberculosis complex test positive, blurred vision/ visual acuity reduced, and glioblastoma multiforme in the adalimumab group, and acute hepatitis in the placebo group.

Adverse events occurring in 38.7% (46 of 119) of subjects in the adalimumab group and 29.2% (35 of 120) of subjects in the placebo group were considered to be “related” or “probably related” to the study drug (“adverse drug reactions”).

Table 7. Adverse events occurring in ≥3% of subjects in adalimumab group (overall study population, safety analysis population)

Event	Adalimumab (N = 119)	Placebo (N = 120)
Nasopharyngitis	21 (17.6)	11 (9.2)
Headache	13 (10.9)	16 (13.3)
Fatigue	12 (10.1)	7 (5.8)
Uveitis	12 (10.1)	8 (6.7)
Arthralgia	10 (8.4)	12 (10.0)
Insomnia	9 (7.6)	8 (6.7)
Back pain	9 (7.6)	3 (2.5)
Eye pain	9 (7.6)	2 (1.7)
Blurred vision	8 (6.7)	2 (1.7)
Bronchitis	7 (5.9)	4 (3.3)
Muscle spasm	7 (5.9)	4 (3.3)
Cough	7 (5.9)	4 (3.3)
Hyperhidrosis	7 (5.9)	3 (2.5)
Urinary tract infection	7 (5.9)	0
Nausea	6 (5.0)	7 (5.8)
Dry mouth	6 (5.0)	1 (0.8)
Anxiety	6 (5.0)	0
Paresthesia	6 (5.0)	0
Oropharyngeal pain	5 (4.2)	5 (4.2)
Acne	5 (4.2)	5 (4.2)
Vitreous floaters	5 (4.2)	4 (3.3)
Upper respiratory tract infection	5 (4.2)	4 (3.3)
Pruritus	5 (4.2)	3 (2.5)
Oedema peripheral	5 (4.2)	2 (1.7)
Myalgia	5 (4.2)	2 (1.7)
Dyspnoea	4 (3.4)	4 (3.3)
Rash	4 (3.4)	4 (3.3)
Dry eye	4 (3.4)	4 (3.3)
Visual acuity reduced	4 (3.4)	3 (2.5)
Blood creatinine increased	4 (3.4)	2 (1.7)
Sinusitis	4 (3.4)	1 (0.8)
Tremor	4 (3.4)	1 (0.8)
Hypertension	4 (3.4)	1 (0.8)
Palpitations	4 (3.4)	1 (0.8)
Pyrexia	4 (3.4)	0

n (%)

In the Japanese subgroup, adverse events occurred in 87.5% (7 of 8) of subjects in the adalimumab group and 87.5% (7 of 8) of subjects in the placebo group. Major event in the adalimumab group was insomnia (50.0% [4 of 8] of subjects in the adalimumab group and 0% of subjects in the placebo group).

There were no deaths or adverse events led to discontinuation. A serious adverse event occurred in 1 subject in the adalimumab group (ureteral calculus). A causal relationship between the investigational drug and this event was ruled out by the investigator. Its outcome was “not resolved.” An adverse drug reaction was observed in 1 subject in the adalimumab group (paronychia).

7.2 Phase III study (CTD 5.3.5.1-2, Study M10-880 [August 2010 to May 2015])

A randomized, double-blind, placebo-controlled, parallel group study was conducted in 22 countries, including the US, Belgium, and Japan, to evaluate the efficacy and safety of adalimumab in patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis[8)] whose disease activity had been controlled by oral steroids at a fixed dose and who had a history of treatment failure due to dose reduction of oral steroid (target sample size, 220 non-Japanese and 30 Japanese patients).

Subjects were stratified by Japanese or non-Japanese subjects. Non-Japanese subjects were stratified by use of baseline immunosuppressive therapy. A total of 261 subjects were randomly allocated to the placebo group or adalimumab group (131 in the adalimumab group, 130 in the placebo group). All of the 261 subjects treated with the study drug were included in the safety analysis population. Of the 261 randomized subjects, 258 subjects (131 in the adalimumab group and 127 in the placebo group) was included in the ITT population. The remaining 3 subjects was excluded from analyses for reasons such as non-compliance with the GCP. The ITT population was used for the efficacy analysis. The study treatment was discontinued in 11.5% (15 of 131) of subjects in the adalimumab group and 13.4% (17 of 127) of subjects in the placebo group. Main reasons for discontinuation included adverse events (in 8.4% [11 of 131] of the subjects in the adalimumab group and 5.5% [7 of 127] of the subjects in the placebo group). In the Japanese subgroup, the study treatment was discontinued in 1 subject in the adalimumab group (adverse events) and 1 subject in the placebo group (deviation from the protocol).

Subjects received an initial dose of 80 mg of adalimumab or placebo by subcutaneous injection, followed by 40 mg or placebo once every 2 weeks starting at 1 week after the initial dose until the end of the study. The maximum duration of study was 80 weeks. In accordance with the protocol, subjects were to undergo tapering of the loading prednisone dose (16.0 ± 7.2 mg/day in the placebo group and 15.3 ± 7.2 mg/day in the adalimumab group [mean ± SD]).[9)]

The primary endpoint of the study was the time to treatment failure[7] at or after Week 2 for the overall study population and the Japanese subgroup. Table 8 shows the results of the primary endpoint. Figures 3 and 4 show the Kaplan-Meier curves. The pairwise comparison of the overall adalimumab group and the overall placebo group exhibited statistically significant differences, demonstrating the superiority of adalimumab to placebo. Because this study was designed to allow patients with uveitis controlled by oral steroids to undergo tapering of the prednisone dose starting 1 week after its initial dose, events were tabulated starting at Week 2, which was the initial endpoint.

---

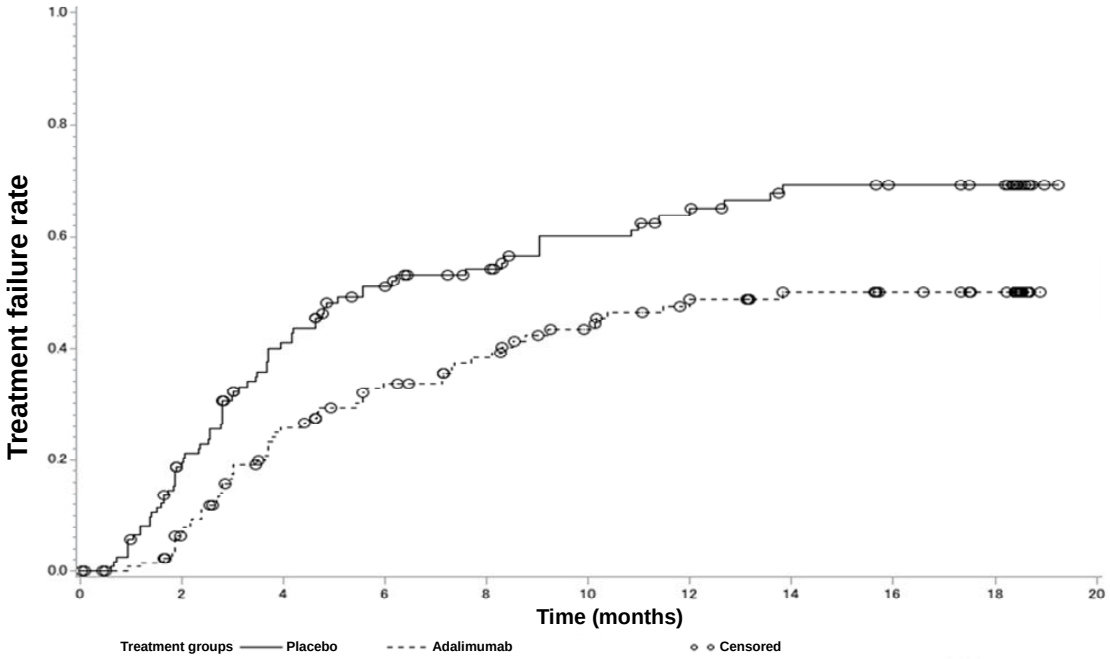
8) Patients who met all the following criteria: (a)on oral steroids at a fixed prednisone-equivalent dose ≥10 mg/day and ≤35 mg/day at baseline (no dose increase for ≤28 days or dose reduction for ≤14 days prior to baseline), (b) no disease activity at ≥28 days prior to the baseline, (c) physician's judgment (at screening and baseline) of anterior chamber cell grade (SUN criteria) ≤0.5+ or vitreous haze grade ≤0.5+ (NEI/SUN criteria), and no active and inflammatory chorioretinal or retinal vascular lesions, (d) failure to taper the oral steroid dose due to flare of disease symptoms within the past 18 months

9) The protocol specified that the dose was tapered weekly from the initial dose to 0 mg/day over 13 to 18 weeks, with no prednisone administered thereafter.

Table 8. Time to treatment failure at or after Week 2 (ITT population)

		Adalimumab	Placebo
Overall study population	Proportion of subjects who had treatment failure during the study period	43.5 (57/131)	59.1 (75/127)
	Median time to treatment failure (months)	Cannot be estimated	5.6
	Hazard ratio [95% CI][a)]	0.52 [0.37, 0.74]	
	P value[a)]	<0.001	
Japanese	Proportion of subjects who had treatment failure during the study period	75.0 (12/16)	87.5 (14/16)
	Median time to treatment failure (months)	2.9	2.1
	Hazard ratio [95% CI][b)]	0.45 [0.20, 1.03]	

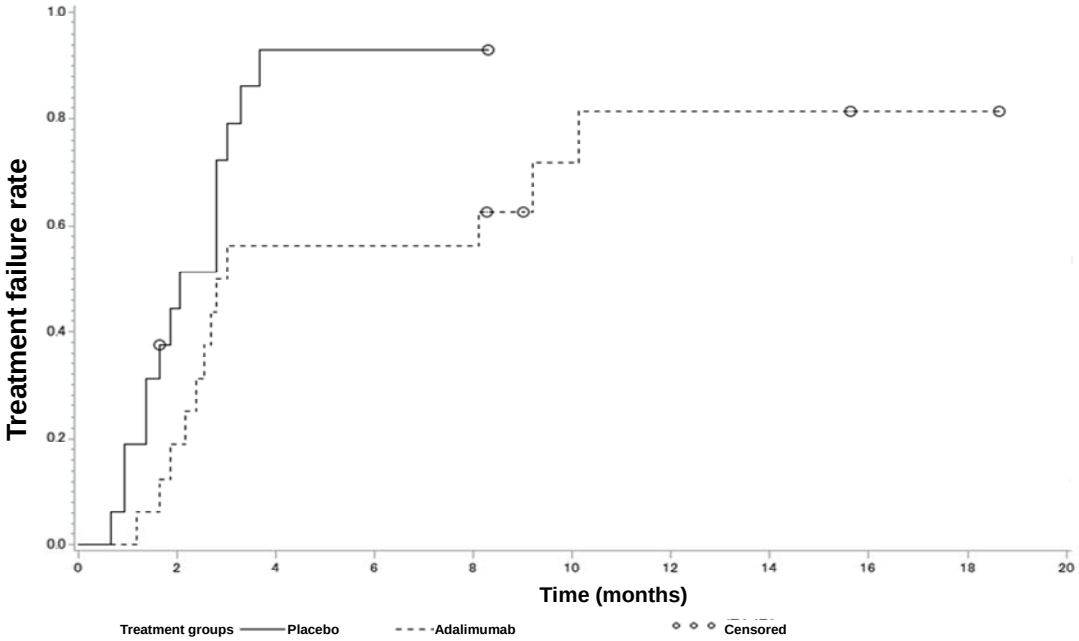
% (n)
a) Cox proportional hazards model using treatment group and Japanese/non-Japanese as explanatory variables
b) Cox proportional hazards model using treatment group as an explanatory variable



Time (months)	0	2	4	6	8	10	12	14	16	18	20
Placebo	0/127	23/97	49/67	60/51	63/42	68/33	72/26	75/21	75/19	75/17	75/0
Adalimumab	0/131	8/118	32/89	41/74	46/65	51/54	56/44	57/39	57/35	57/31	57/0

(Cumulative number of subjects who had treatment failure/number of subjects at risk)

Figure 3. Kaplan-Meier curve of treatment failure at or after Week 2 (overall study population, ITT population)



Time (months)	0	2	4	6	8	10	12	14	16	18	20
Placebo	0/16	7/8	14/1	14/1	14/1	14/0	14/0	14/0	14/0	14/0	14/0
Adalimumab	0/16	3/13	9/7	9/7	9/7	11/3	12/2	12/2	12/1	12/1	12/0

(Cumulative number of subjects with treatment failure/number of subjects at risk)

Figure 4. Kaplan-Meier curve of treatment failure at or after Week 2 (Japanese subgroup, ITT population)

Analyses in the overall study population revealed adverse events occurring in 89.3% (117 of 131) of the subjects in the adalimumab group and 81.5% (106 of 130) of subjects in the placebo group. Table 9 lists major adverse events. There was 1 death in the adalimumab group (cardiac tamponade/aortic dissection). A causal relationship between this event and the study drug was ruled out.

Serious adverse events occurred in 6.9% (9 of 131) of the subjects in the adalimumab group (cataract, stage IV lung adenocarcinoma, pneumonia/neutropenia, cardiac tamponade/aortic dissection, transient blindness/dysphagia/dysarthria, bronchitis/pleuritis/pneumonia legionella, fibula fracture, status migrainosus, and epistaxis in 1 subject each) and 7.7% (10 of 130) of the subjects in the placebo group (osteonecrosis and deep vein thrombosis in 2 subjects each and choroidal neovascularization/subretinal fluid, retinal detachment, aseptic meningitis, tonsillitis, humerus fracture, arthritis, and hypertensive crisis in 1 subject each). Among them, adverse events for which a causal relationship to the study drug could not be ruled out by the investigator were stage IV lung adenocarcinoma, pneumonia legionella, and neutropenia in the adalimumab group and hypertension crisis and tonsillitis in the placebo group. Stage IV lung adenocarcinoma and pneumonia legionella remained unresolved.

Adverse events led to discontinuation in 8.4% (11 of 131) of the subjects in the adalimumab group (Mycobacterium tuberculosis complex test positive in 3 subjects, drug eruption, neutropenia, cardiac tamponade/aortic dissection, hepatic steatosis, bronchitis, status migrainosus, pulmonary sarcoidosis and dermatitis in 1 subject each) and 5.4% (7 of 130) of the subjects in the placebo group (colour blindness acquired, macular oedema, Mycobacterium tuberculosis complex test positive, adenomatous polyposis, pulmonary sarcoidosis, allergic dermatitis, and rash macular). Among them, adverse events

for which a causal relationship to the study drugs could not be ruled out by the investigator were the events in 5 subjects in the adalimumab group (drug eruption, Mycobacterium tuberculosis complex test positive, neutropenia, hepatic steatosis, and dermatitis) and those in 4 subjects in the placebo group (Mycobacterium tuberculosis complex test positive, colour blindness acquired, allergic dermatitis, and rash macular). Adverse reactions occurred in 51.1% (67 of 131) of the subjects in the adalimumab group and 40.0% (52 of 130) of the subjects in the placebo group.

Table 9. Adverse events occurring in ≥3% of subjects in adalimumab group (overall study population, safety analysis population)

Event	Adalimumab (N = 131)	Placebo (N = 130)
Arthralgia	28 (21.4)	12 (9.2)
Nasopharyngitis	23 (17.6)	20 (15.4)
Headache	17 (13.0)	17 (13.1)
Fatigue	14 (10.7)	9 (6.9)
Urinary tract infection	13 (9.9)	11 (8.5)
Cough	11 (8.4)	6 (4.6)
Back pain	10 (7.6)	7 (5.4)
Upper respiratory tract infection	10 (7.6)	3 (2.3)
Pain in extremity	10 (7.6)	3 (2.3)
Eye pain	9 (6.9)	6 (4.6)
Insomnia	9 (6.9)	3 (2.3)
Increased alanine aminotransferase	9 (6.9)	1 (0.8)
Injection site pain	8 (6.1)	9 (6.9)
Sinusitis	8 (6.1)	4 (3.1)
Increased aspartate aminotransferase	8 (6.1)	1 (0.8)
Cystoid macular oedema	7 (5.3)	7 (5.4)
Hypertension	7 (5.3)	5 (3.8)
Visual acuity reduced	6 (4.6)	10 (7.7)
Uveitis	6 (4.6)	9 (6.9)
Pyrexia	6 (4.6)	8 (6.2)
Myalgia	6 (4.6)	2 (1.5)
Injection site rash	6 (4.6)	1 (0.8)
Dry eye	5 (3.8)	8 (6.2)
Vitreous floaters	5 (3.8)	6 (4.6)
Rash	5 (3.8)	5 (3.8)
Alopecia	5 (3.8)	5 (3.8)
Neck pain	5 (3.8)	3 (2.3)
Oropharyngeal pain	5 (3.8)	3 (2.3)
Pruritus	5 (3.8)	2 (1.5)
Swollen joint	5 (3.8)	2 (1.5)
Anxiety	5 (3.8)	2 (1.5)
Erythema	5 (3.8)	2 (1.5)
Malaise	5 (3.8)	2 (1.5)
Intraocular pressure increased	5 (3.8)	2 (1.5)
Nasal congestion	5 (3.8)	1 (0.8)
Pharyngitis	5 (3.8)	1 (0.8)
Pustular skin eruption	5 (3.8)	0
Nausea	4 (3.1)	9 (6.9)
Diarrhea	4 (3.1)	9 (6.9)
Blurred vision	4 (3.1)	6 (4.6)
Vomiting	4 (3.1)	4 (3.1)
Musculoskeletal stiffness	4 (3.1)	4 (3.1)
Dyspnoea	4 (3.1)	3 (2.3)
Ear pain	4 (3.1)	2 (1.5)
Tinnitus	4 (3.1)	2 (1.5)
Eczema	4 (3.1)	2 (1.5)
Conjunctivitis	4 (3.1)	2 (1.5)
Gastroenteritis	4 (3.1)	2 (1.5)
Paresthesia	4 (3.1)	1 (0.8)
Palpitations	4 (3.1)	1 (0.8)
Macular oedema	4 (3.1)	1 (0.8)
Peripheral oedema	4 (3.1)	1 (0.8)
Sarcoidosis	4 (3.1)	1 (0.8)
Epistaxis	4 (3.1)	0

n (%)

Analyses in the Japanese subgroup revealed adverse events occurring in 75.0% (12 of 16) of the subjects in the adalimumab group and 62.5% (10 of 16) of the subjects in the placebo group. Major adverse events in the adalimumab group were nasopharyngitis (31.3% [5 of 16] of the subjects in the adalimumab group and 6.3% [1 of 16] of the subjects in the placebo group), macular oedema, increased aspartate aminotransferase, and increased intraocular pressure (all of which occurred in 12.5% [2 of 16] of the subjects in the adalimumab group and 0% in the placebo group).

There were no deaths. Serious adverse events occurred in 2 subjects in the adalimumab group (cataract and stage IV lung adenocarcinoma) and 1 subject in the placebo group (osteonecrosis). A causal relationship to the study drug could not be ruled out by the investigator for stage IV lung adenocarcinoma reported in the adalimumab group. Its outcome was "not resolved."

An adverse event led to discontinuation in 1 subject in the adalimumab group (drug eruption). A causal relationship between this event and the study drug could not be ruled out by the investigator. Adverse reactions occurred in 3 subjects in the adalimumab group (drug eruption/stage IV lung adenocarcinoma, injection site rash, and pyrexia).

7.R Outline of the review conducted by PMDA

7.R.1 Protocol, etc. of Phase III studies

7.R.1.1 Protocol

The applicant's explanation about the protocol of the Phase III studies:

The applicant decided to conduct confirmatory studies (Studies M10-877 and M10-880) in patients with non-infectious uveitis in various countries, including Japan, and to use their results as the pivotal study data for regulatory submission in Japan. The above decision is based on the following reasons: (1) There are no great differences in diagnosis, drug therapies, medical environment, or other aspects of non-infectious uveitis between Japanese and non-Japanese patients; (2) the limited number of Japanese patients with uveitis precludes randomized, placebo-controlled, parallel group studies from being conducted only in Japan; and (3) although non-infectious uveitis is classified into various disease types such as idiopathic uveitis, differences in the etiology of uveitis are unlikely to affect the efficacy of TNF-α inhibitors (*J Ocul Pharmacol Ther.* 2008;24:351-61, *Arch Ophthalmol.* 2005;123:903-12).

However, the distribution of various types of non-infectious uveitis tends to differ between Japan on the one hand and in the US and Europe on the other. Specifically, while the prevalence of idiopathic uveitis is considered to be high both in and outside of Japan, the prevalence of uveitis associated with Behcet's disease or Vogt-Koyanagi-Harada syndrome tends to be higher in Japan than in the US and Europe (*Eur J Ophthalmol.* 2013;23:705-17, *Jpn J Ophthalmol.* 2012;56:432-5). Since such differences in the distribution of various types of non-infectious uveitis were pointed out by other regulatory authorities, the applicant decided to exclude the Japanese subgroup from the primary analyses of Studies M10-877 and M10-880 for regulatory submission outside of Japan. Data from this subgroup were deemed to be sub-study data, and data from the non-Japanese subgroup were analyzed

as the main study. An application was submitted based on the results of analyses of the main study data.

Although data from the non-Japanese subgroup were analyzed as the main study and data from the Japanese subgroup as the sub-study in Studies M10-877 and M10-880, PMDA decided to evaluate the efficacy and safety of adalimumab in Japanese patients with intermediate uveitis, posterior uveitis, or panuveitis based on the data from the overall study population in Studies M10-877 and M10-880, considering the following points:

- Data from the Japanese subgroup and non-Japanese subgroup were obtained from the studies which were conducted in accordance with the same double-blind study protocol and in which database locking and unblinding were also performed accordingly.
- Analyses of data from the overall study population were planned in advance for the regulatory submission in Japan.
- The differences in the etiology of uveitis are unlikely to affect the efficacy of TNF-α inhibitors, although the number of patients evaluated is limited (*J Ocul Pharmacol Ther.* 2008;24:351-61, *Arch Ophthalmol.* 2005;123:903-12).

7.R.1.2 Subjects of Phase III studies

The applicant's explanation about subjects eligible for enrollment in Phase III studies:

Steroids play a central role in the treatment of non-infectious uveitis because of their prompt effects. Systemic steroid therapies including oral steroids are used for the treatment of intermediate uveitis, posterior uveitis, and panuveitis. Since additional treatment with an immunosuppressive agent is recommended when oral steroid (≥10 mg of prednisone or equivalent per day) is needed as the maintenance dose to control disease activity (*Am J Ophthalmol.* 2000;130:492-513), patients with inadequate response to steroid therapy (i.e., those with active uveitis despite ≥2 weeks of oral steroid treatment at a dose of ≥10 mg prednisone or equivalent per day) were enrolled in Study M10-877 for active uveitis. Study M10-880 for inactive uveitis included patients who had to receive the maintenance dose of oral steroids to control disease activity (i.e., those who experienced a disease flare after tapering of oral steroids and then failed tapering due to the flare and who were on oral steroid therapy at a dose of ≥10 to ≤35 mg prednisone or equivalent per day before the start of treatment with adalimumab). Patients with refractory uveitis were eligible for enrollment in both studies. Study M10-877 included patients with inadequate response to oral steroid therapy who were considered to require additional treatment. Study M10-880 included patients who were considered to require additional treatment to reduce the dose of oral steroids.

PMDA's comment:

As explained by the applicant, Study M10-877 included patients with active uveitis refractory to oral steroids and Study M10-880 included patients with inactive uveitis on high-dose oral steroids.

Accordingly, both studies were conducted in patients with inadequate response to low-dose oral steroids.

7.R.1.3 Primary endpoint

The applicant's explanation about the primary efficacy endpoint of Phase III studies:

In Studies M10-877 and M10-880, treatment failure was defined as the conditions meeting at least one of the following criteria, and time to treatment failure was selected as the primary endpoint to compare placebo and adalimumab.

- New inflammatory chorioretinal lesions and/or retinal vascular lesions
- 2-step increase in anterior chamber cell grade (SUN criteria)
- 2-step increase in vitreous haze grade (NEI/SUN criteria)
- Worsening of best-corrected visual acuity (BCVA) by ≥15 letters

In patients with uveitis, flares of ocular inflammation are known to lead to gradual progression of irreversible eye injuries (*Am J Ophthalmol.* 2015;160:1133-41). Thus, treatment goals for uveitis should include the prevention of disease flares (treatment failure) and the reduction of the degree and area of inflammation, which are considered essential for preventing the deterioration of visual function. For this reason, time to treatment failure was selected as the primary endpoint. Time to treatment failure was defined by the pathological criteria (new inflammatory lesions and increases in vitreous haze grade or anterior chamber cell grade) which were considered clinically relevant for the long-term preservation of visual function and the visual function-related criterion (worsening of BCVA by ≥15 letters). Prolongation of time to treatment failure defined by these criteria directly indicates the prevention of deterioration of visual function or indirectly represents a reduced risk of visual impairment resulting from the improvement of clinical conditions such as inflammation. Prolonged time to treatment failure is therefore considered clinically relevant for the long-term preservation of visual function.

PMDA's view:

The applicant's explanation is acceptable. The efficacy of adalimumab in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis can be evaluated based on the proposed primary endpoint.

7.R.2 Efficacy

PMDA's view:

On the basis of the review of data from the Japanese subgroup presented in Section 7.R.2.2, PMDA has determined that the efficacy of adalimumab can be evaluated using the data from the overall study population. In addition, adalimumab can be expected to be effective in Japanese patients with non-infectious uveitis, because its efficacy was demonstrated in the overall study population (see Section

7.R.2.1). However, because of the limited number of Japanese patients evaluated, the efficacy of adalimumab should be further investigated in a post-marketing surveillance study.

A final decision on the efficacy of adalimumab will be made based on the comments raised in the Expert Discussion.

7.R.2.1 Results in overall study population

The applicant's explanation about the efficacy of adalimumab in the overall study population:
Time to treatment failure (the primary endpoint) was assessed to demonstrate the efficacy of adalimumab in the overall study population in both Studies M10-877 and M10-880 [see Section "7.1 Phase III study" and Section "7.2 Phase III study"]. Results for the criteria suggested that adalimumab prolonged time to treatment failure (see Table 10).

Table 10. Efficacy data for each parameters of criteria for treatment failure in the overall study population in Study M10-877 and Study M10-880

	Hazard ratio of adalimumab to placebo[a)] [95% CI]	
	Study M10-877	Study M10-880
New inflammatory chorioretinal lesions and/or retinal vascular lesions	0.56 [0.33, 0.95]	0.45 [0.23, 0.85]
2-step increase in anterior chamber cell grade (SUN criteria)	0.51 [0.30, 0.86]	0.66 [0.41, 1.05]
2-step increase in vitreous haze grade (NEI/SUN criteria)	0.35 [0.20, 0.60]	0.46 [0.21, 0.98]
Worsening of BCVA by ≥15 leters	0.57 [0.33, 0.98]	0.33 [0.17, 0.65]

a) Cox proportional hazards model using treatment group and Japanese/non-Japanese as explanatory variables

Table 11 shows the subgroup analysis by etiology and inflammation site of uveitis. Although some subgroups are difficult to evaluate due to the small number of subjects, the efficacy of adalimumab did not differ greatly by etiology or inflammation site of uveitis.

Table 11. Efficacy by subgroup (etiology, inflammation site of uveitis) in Study M10-877 and Study M10-880

		Study M10-877		Study M10-880	
		Number of subjects	Hazard ratio of adalimumab to placebo[a] [95% CI]	Number of subjects	Hazard ratio of adalimumab to placebo[a] [95% CI]
Etiologic diagnosis	Idiopathic/other	62 in placebo group 48 in adalimumab group	0.56 [0.35, 0.88]	54 in placebo group 45 in adalimumab group	0.44 [0.25, 0.77]
	Birdshot chorioretinopathy	20 in placebo group 24 in adalimumab group	0.49 [0.21, 1.14]	15 in placebo group 15 in adalimumab group	0.57 [0.10, 3.11]
	Multifocal choroiditis/panuveitis	3 in placebo group 8 in adalimumab group	0.60 [0.11, 3.35]	2 in placebo group 5 in adalimumab group	0.17 [0.02, 1.93]
	Vogt-Koyanagi-Harada syndrome	14 in placebo group 12 in adalimumab group	0.77 [0.32, 1.82]	29 in placebo group 34 in adalimumab group	0.69 [0.37, 1.30]
	Sarcoidosis	12 in placebo group 12 in adalimumab group	0.50 [0.18, 1.43]	20 in placebo group 22 in adalimumab group	1.09 [0.49, 2.41]
	Behcet's disease	4 in placebo group 14 in adalimumab group	0.83 [0.17, 4.15]	7 in placebo group 10 in adalimumab group	- [b]
Inflammation site of uveitis	Intermediate uveitis	23 in placebo group 25 in adalimumab group	0.81 [0.41, 1.57]	30 in placebo group 17 in adalimumab group	0.63 [0.29, 1.40]
	Posterior uveitis	37 in placebo group 38 in adalimumab group	0.39 [0.20, 0.75]	35 in placebo group 41 in adalimumab group	0.95 [0.45, 2.03]
	Panuveitis	55 in placebo group 55 in adalimumab group	0.52 [0.33, 0.82]	61 in placebo group 71 in adalimumab group	0.46 [0.29, 0.73]

a) Cox proportional hazards model using treatment group and Japanese/non-Japanese as explanatory variables
b) Not calculated because of no subjects with treatment failure in the adalimumab group

The subjects who completed 80 weeks of treatment in Study M10-877 or Study M10-880 and the subjects who experienced treatment failure during the study period were allowed to participate in the open-label, uncontrolled, extension study (Study M11-327). The long-term efficacy of adalimumab has been demonstrated by the following results from Study M11-327.

- The dose of oral steroid in Study M11-327 was allowed to be increased or decreased by the investigator at his/her clinical discretion. The steroid dose (mean ± SD) in patients who had active uveitis at the time of entry into Study M11-327 was changed to 13.8 ± 16.6 mg/day (n = 237) at Week 2, 3.8 ± 7.1 mg/day (n = 160) at Week 54, and 2.3 ± 4.7 mg/day (n = 83) at Week 102. The steroid dose in patients who had inactive uveitis at the time of entry into Study M11-327 was changed to 1.6 ± 6.6 mg/day (n = 126) at Week 2, 0.1 ± 0.7 mg/day (n = 35) at Week 54, and 0.3 ± 1.1 mg/day (n = 19) at Week 102. These results showed that long-term treatment with adalimumab enabled tapering of oral steroids.
- Table 12 shows the proportion of subjects without new active lesions, proportion of subjects with anterior chamber cell grade ≤0.5, and proportion of subjects with vitreous haze grade ≤0.5, which are results from Study M11-327. The results demonstrated the long-term efficacy of adalimumab.

Table 12. Changes in endpoints of Study M11-327

Endpoint	Disease activity at entry into Study M11-327[b)]	Week 54[c)]	Week 102[c)]
Proportion of subjects without new active lesions (%)[a)]	Active uveitis	98.1 (152/155)	97.5 (79/81)
	Inactive uveitis	97.1 (33/34)	100 (17/17)
Proportion of subjects with anterior chamber cell grade ≤0.5 (%)	Active uveitis	91.1 (143/157)	91.4 (74/81)
	Inactive uveitis	100 (34/34)	100 (17/17)
Proportion of subjects with vitreous haze grade ≤0.5 (%)	Active uveitis	84.0 (131/156)	91.4 (74/81)
	Inactive uveitis	88.2 (30/34)	88.2 (15/17)

% (n/N)
a) For subjects with active uveitis, the proportion of subjects not showing new lesions compared to Week 8
b) Subjects were divided by treatment outcome in Study M10-877 or M10-880. Patients with and without treatment failure were enrolled in Study M11-327 as subjects with active uveitis and those with inactive uveitis, respectively.
c) The analysis included subjects who had completed the study treatment at the data cutoff point in April 2015

PMDA's view:

Because the superiority of adalimumab to placebo has been demonstrated in Study M10-877 and Study M10-880, the study data can support the efficacy of adalimumab for non-infectious uveitis. There are no particular problems with the long-term efficacy of adalimumab. On the basis of the results of subgroup analysis, adalimumab can be expected to be effective for all types of uveitis (intermediate uveitis, posterior uveitis, and panuveitis), regardless of uveitis disease etiology.

7.R.2.2 Results in Japanese subgroup

Table 13 shows efficacy results in the overall study population versus the Japanese subgroup. Study M10-877 did not show consistency between the overall study population and the Japanese subgroup. PMDA asked the applicant to explain the reason for the lack of consistency in Study M10-877.

The applicant's response:

In Study M10-877, 19 events of treatment failure were predicted to be necessary in the Japanese subgroup to demonstrate consistency in outcomes between the overall study population and the Japanese subgroup. Thus, the target sample size of 32 was selected for Japanese subjects. However, 16 Japanese subjects were enrolled eventually, and Study M10-877 ended when 14 subjects experienced treatment failure.[10)] The number of events in the Japanese subjects enrolled in Study M10-877 was not large enough to evaluate consistency in efficacy outcomes between the overall study population and the Japanese subgroup. Therefore, the lack of consistency may have been incidental. One of the reasons for insufficient recruitment of Japanese subjects was a safety concern regarding the use of high-dose steroids. In Study 10-877, subjects were to receive an initial dose of 60 mg/day of an oral steroid and were to undergo a mandatory tapering schedule over 15 weeks. The steroid dose may have been higher than the standard dose of oral steroids used for the treatment of uveitis in Japan.

PMDA's view:

The limited number of events in Japanese subjects in Study M10-877 precluded evaluation of the consistency in results between the overall study population and the Japanese subgroup; this reasoning is understandable. In light of the following points, the data from the Japanese subgroup in Study M10-

[10)] The protocol pre-specified that Study M10-877 would end at Week 80 or at the time when the target number of treatment failures (138 events) have been reached in non-Japanese subjects or the target numbers of treatment failures (19 events) in the Japanese subgroup. Because the number of treatment failures in non-Japanese subjects reached 138, the study was terminated.

877 still support the efficacy of adalimumab, and the efficacy of adalimumab can be evaluated based on the results in the overall study population of Study M10-877 and Study M10-880.

- Table 13 shows the hazard ratio of adalimumab to placebo and its 95% CI for each parameter of the treatment failure criteria in the overall study population of Study M10-877. Analyses revealed a trend toward a reduced risk of events in adalimumab-treated subjects in terms of all the parameters of the criteria (active inflammatory lesions, anterior chamber cell grade, vitreous haze grade, and logMAR BCVA). In the Japanese subgroup, the hazard ratio for active inflammatory lesions was 3.07 [0.62, 15.20], which exceeded 1, while those for vitreous haze grade and logMAR BCVA were 0.53 [0.13, 2.14] and 0.61 [0.06, 6.86], respectively, showing a tendency toward a reduced risk of the events.
- Subgroup analyses were performed by patient characteristics to assess differences between the overall study population and the Japanese subgroup. Differences were found in term of not only disease etiology and type of uveitis, but also the duration of flare at screening (≥60 days: 38.6% [90 of 233 subjects] in the overall study population, 68.8% [11 of 16 subjects] in the Japanese subgroup) in Study M10-877 and the dose of prednisone at the last flare (≥10 mg/day: 42.2% [109 of 258 subjects] in the overall study population, 68.7% [22 of 32 subjects] in the Japanese subgroup) and use of concomitant immunosuppressive agents (subjects with use of such agents: 47.3% [107 of 258 subjects] in the overall study population, 9.4% [3 of 32 subjects] in the Japanese subgroup) in Study M10-880. As shown in Tables 11 and 14, however, the differences in the patient characteristics did not affect the efficacy of adalimumab.
- As shown in Table 13, data from Study M10-880 showed consistency in outcomes between the overall study population and the Japanese subgroup.
- As shown in Table 15, the long-term efficacy of adalimumab was also demonstrated in the Japanese subgroup in the long-term extension study (Study M11-327).

Table 13. Efficacy in overall study population and Japanese subgroup by treatment failure criteria in Study M10-877 and Study M10-880

	Hazard ratio of adalimumab to placebo[a)] [95% CI]			
	Study M10-877		Study M10-880	
	Overall study population	Japanese subgroup	Overall study population	Japanese subgroup
Meeting any of the following criteria (primary endpoint)	0.56 [0.40, 0.76]	1.20 [0.41, 3.54]	0.52 [0.37, 0.74]	0.45 [0.20, 1.03]
New inflammatory chorioretinal lesions and/or retinal vascular lesions	0.56 [0.33, 0.95]	3.07 [0.62, 15.20]	0.45 [0.23, 0.85]	0.41 [0.12, 1.42]
2-step increase in anterior chamber cell grade (SUN criteria)	0.51 [0.30, 0.86]	-	0.66 [0.41, 1.05]	0.68 [0.24, 1.92]
2-step increase in vitreous haze grade (NEI/SUN criteria)	0.35 [0.20, 0.60]	0.53 [0.13, 2.14]	0.46 [0.21, 0.98]	-
Worsening of BCVA by ≥15 letters	0.57 [0.33, 0.98]	0.61 [0.06, 6.86]	0.33 [0.17, 0.65]	0.20 [0.02, 1.77]

a) Cox proportional hazards model using treatment group and Japanese/non-Japanese as explanatory variables in the analysis of data from the overall study population, Cox proportional hazards model using treatment group as an explanatory variable in the analysis of data from the Japanese subgroup

- Not calculated due to the small number of events

Table 14. Hazard ratio for time to treatment failure by subgroup in Study M10-877 and Study M10-880

		Study M10-877		Study M10-880	
		Number of subjects	Hazard ratio of adalimumab to placebo[a] [95% CI]	Number of subjects	Hazard ratio of adalimumab to placebo[a] [95% CI]
Use of concomitant immunosuppressive agent	Yes	35 in placebo group 35 in adalimumab group	0.59 [0.33, 1.08]	54 in placebo group 56 in adalimumab group	0.51 [0.27, 0.95]
	No	80 in placebo group 83 in adalimumab group	0.53 [0.37, 0.78]	73 in placebo group 75 in adalimumab group	0.61 [0.40, 0.92]
Duration of flare at screening	≥60 days	48 in placebo group 42 in adalimumab group	0.54 [0.32, 0.92]		
	<60 days	67 in placebo group 76 in adalimumab group	0.55 [0.37, 0.83]		
Dose of prednisone at the last flare	<10 mg/day			73 in placebo group 76 in adalimumab group	0.68 [0.42, 1.09]
	≥10 mg/day			54 in placebo group 55 in adalimumab group	0.45 [0.28, 0.75]

a) Cox proportional hazards model using treatment group and Japanese/non-Japanese as explanatory variables

Table 15. Changes in endpoints in Japanese subgroup in Study M11-327

Endpoint	Disease activity at entory into Study M11-327[c]	Week 12[d]	Week 54[d]
Dose of oral steroid (mg/day)[a]	Active uveitis	7.4 ± 7.3	5.3 ± 5.3
	Inactive uveitis	2.7 ± 5.4	1.3 ± 2.5 [e]
Proportion of subjects without new active lesions (%)[b]	Active uveitis	96.7 (29/30)	100 (19/19)
	Inactive uveitis	100 (4/4)	100 (4/4) [e]
Proportion of subjects with anterior chamber cell grade ≤0.5 (%)	Active uveitis	86.7 (26/30)	89.5 (17/19)
	Inactive uveitis	100 (4/4)	100 (4/4) [e]
Proportion of subjects with vitreous haze grade ≤0.5 (%)	Active uveitis	73.3 (22/30)	73.7 (14/19)
	Inactive uveitis	75.0 (3/4)	75.0 (3/4) [e]

Mean ± SD, or % (n/N)
a) The dose of oral steroids at Week 2 was 13.3 ± 8.7 mg/day for active uveitis and 2.9 ± 7.6 mg/day for inactive uveitis.
b) For subjects with active uveitis, the proportion of subjects free of new lesions compared to Week 8
c) Subjects were divided by treatment outcome in Study M10-877 or Study M10-880. Patients with and without treatment failure were enrolled in Study M11-327 as subjects with active uveitis and those with inactive uveitis, respectively.
d) The anlysis included subjects who had completed the study treatment at the data cutoff point in April 2015
e) Data at Week 42

7.R.3 Safety

7.R.3.1 Safety in approved indication and safety in uveitis

The applicant assessed the safety of adalimumab by comparing the results of Japanese clinical studies with the approved indications (rheumatoid arthritis, 6 studies; psoriasis vulgaris and psoriatic arthritis, 2 studies; ankylosing spondylitis, 1 study; juvenile idiopathic arthritis, 1 study; intestinal Behcet's disease, 1 study; Crohn's disease, 2 studies; ulcerative colitis, 1 study) and the results of clinical studies in patients with non-infectious uveitis.

The applicant's explanation:

Table 16 summarizes the adverse events reported in the study of each disease. The incidence of adverse events in Japanese patients with non-infectious uveitis was 91.3% (42 of 46 subjects); the incidence of serious adverse events was 28.3% (13 of 46 subjects), showing no tendency toward higher incidence than that for the approved indications. Analysis of the incidences of adverse events listed in the package insert of adalimumab (serious infection, malignant tumor, tuberculosis, lupus-like syndrome, demyelinating disease, allergic reaction, blood disorder, and hepatic dysfunction) showed no trends toward significant differences in the incidences of adverse events between clinical studies for the approved indications and clinical studies for uveitis. Adverse events classified as eye disorders (system organ class [SOC]) tended to be more common in patients with non-infectious uveitis (54.3% [25/46

subjects]) than in patients evaluated in clinical studies for the approved indications (9.2% to 26.8%). However, many of the reported events were associated with uveitis. No additional precautionary advice about the safety of adalimumab is considered necessary.

Table 16. Summary of safety data of adalimumab used for non-infectious uveitis and approved indications

	Uveitis		Rheumatoid arthritis N = 382 755.2 person-year	Psoriasis N = 163 349.6 person-year	Ankylosing spondylitis N = 41 44.0 person-year	JIA[a] N = 25 27.1 person-year	Intestinal BD[b] N = 20 18.2 person-year	Crohn's disease N = 90 70.3 person-year	UC[c] N = 240 189.4 person-year
	Japanese N = 46 80.4 person-year	Japanese and non-Japanese N = 464 796.9 person-year							
Adverse event	42 (91.3) 311 (386.7)	432 (93.1) 4598 (577.0)	376 (98.4) 5258 (696.2)	160 (98.2) 2271 (649.6)	41 (100) 250 (568.2)	25 (100) 200 (738.0)	20 (100) 102 (560.4)	85 (94.4) 685 (974.4)	227 (94.6) 1100 (580.8)
Serious adverse event	13 (28.3) 21 (26.1)	92 (19.8) 156 (19.6)	162 (42.4) 317 (42.0)	21 (12.9) 30 (8.6)	4 (9.8) 7 (15.9)	6 (24.0) 9 (33.2)	1 (5.0) 1 (5.5)	35 (38.9) 46 (65.4)	51 (21.3) 65 (34.3)
Infection	24 (52.2) 76 (94.5)	287 (61.9) 816 (102.4)	290 (75.9) 1086 (143.8)	131 (80.4) 524 (149.9)	25 (61.0) 51 (115.9)	21 (84.0) 79 (291.5)	14 (70.0) 30 (164.8)	65 (72.2) 171 (243.2)	145 (60.4) 283 (149.4)
Serious infection	2 (4.3) 2 (2.5)	29 (6.3) 35 (4.4)	45 (11.8) 67 (8.9)	4 (2.5) 4 (1.1)	2 (4.9) 3 (6.8)	3 (12.0) 3 (11.1)	0 0	6 (6.7) 6 (8.5)	12 (5.0) 13 (6.9)
Malignant tumor	2 (4.3) 2 (2.5)	13 (2.8) 13 (1.6)	11 (2.9) 14 (1.9)	2 (1.2) 2 (0.6)	1 (2.4) 1 (2.3)	0 0	0 0	1 (1.1) 1 (1.4)	3 (1.3) 4 (2.1)
Tuberculosis	0 0	19 (4.1) 19 (2.4)	2 (0.5) 2 (0.3)	1 (0.6) 1 (0.3)	0 0	0 0	1 (5.0) 1 (5.5)	0 0	1 (0.4) 1 (0.5)
Opportunistic infection not including tuberculosis	0 0	2 (0.4) 2 (0.3)	7 (1.8) 9 (1.2)	1 (0.6) 1 (0.3)	1 (2.4) 1 (2.3)	0 0	0 0	1 (1.1) 1 (1.4)	9 (3.8) 9 (4.8)
Injection site reaction	3 (6.5) 3 (3.7)	69 (14.9) 153 (19.2)	136 (35.6) 232 (30.7)	34 (20.9) 56 (16.0)	9 (22.0) 19 (43.2)	6 (24.0) 8 (29.5)	2 (10.0) 2 (11.0)	16 (17.8) 17 (24.2)	26 (10.8) 28 (14.8)
Lupus-like syndrome	0 0	1 (0.2) 1 (0.1)	1 (0.3) 1 (0.1)	1 (0.6) 1 (0.3)	0 0	0 0	0 0	0 0	0 0
Allergic reaction	2 (4.3) 3 (3.7)	35 (7.5) 43 (5.4)	5 (1.3) 5 (0.7)	0 0	0 0	0 0	2 (10.0) 2 (11.0)	2 (2.2) 2 (2.8)	7 (2.9) 7 (3.7)
Demyelinating disease	0 0	6 (1.3) 6 (0.8)	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Blood disorder	0 0	12 (2.6) 17 (2.1)	1 (0.3) 1 (0.1)	0 0	2 (4.9) 2 (4.5)	0 0	0 0	0 0	12 (5.0) 12 (6.3)
Hepatic dysfunction	0 0	6 (1.3) 7 (0.9)	76 (19.9) 134 (17.7)	63 (38.7) 133 (38.0)	13 (31.7) 15 (34.1)	3 (12.0) 3 (11.1)	3 (15.0) 4 (22.0)	16 (17.8) 28 (39.8)	16 (6.7) 18 (9.5)
Congestive heart failure	0 0	0 0	3 (0.8) 4 (0.5)	1 (0.6) 1 (0.3)	0 0	0 0	0 0	0 0	0 0
Adverse events leading to death	0 0	3 (0.6) 4 (0.5)	4 (1.0) 5 (0.7)	0 0	0 0	0 0	0 0	0 0	2 (0.8) 2 (1.1)

Upper row, n (%); lower row, number of events (incidence rate per 100 person-year);
Each event was tabulated by CMQ (Company MedDRA Query).
a) Juvenile idiopathic arthritis
b) Intestinal Behcet's disease
c) Ulcerative colitis

PMDA's view:

The submitted data on the safety of adalimumab in patients with non-infectious uveitis raise no new concerns when compared with data from the clinical studies for the approved indications and other data. However, because the number of Japanese patients with uveitis evaluated is limited, the

occurrence of adverse events including serious infection should be further investigated in a post-marketing surveillance study.

7.R.3.2 Safety in patients with sarcoidosis

Since the current package insert lists sarcoidosis as an adverse reaction, PMDA asked the applicant to explain the safety of adalimumab in patients with uveitis associated with sarcoidosis.

The applicant's explanation:

Sarcoidosis is a multiorgan disease of unknown cause, characterized by non-caseating and granulomatous infiltration in multiple organ systems, including the eyes. TNF-α has been reported to play a role in the pathogenesis of sarcoidosis. For example, TNF-α derived from alveolar macrophage is involved in the formation and progression of granuloma (*Am J Respir Crit Care Med.* 2010;182:540-8). Studies suggest that adalimumab, a TNF-α inhibitor, can be a therapeutic option for systemic sarcoidosis (*J Transl Med.* 2012;8:238-47, *Clin Respir J.* 2012;6:238-47). Nevertheless, several publications have reported the onset of sarcoidosis associated with the use of TNF-α inhibitors including adalimumab (*Clin Exp Rheumatol.* 2008;26:471-5, *Rheumatol.* 2009;48:883-6, and other reports). A hypothesis has been proposed that neutralization of TNF-α results in an imbalance of cytokines, which activates specific autoreactive T cells, consequently causing sarcoidal reaction (*Clin Exp Rheumatol.* 2008;26:471-5, *Respir Med Case Reports.* 2013;10:53-5).

In Studies M10-877 and M10-880, adverse events of sarcoidosis were reported by 6 of 250 subjects (2.4%, 4.8 events per 100 person-year) in the adalimumab groups and 2 subjects (0.8%, 3.3 events per 100 person-year) in the placebo groups. A total of 11 events of sarcoidosis occurred in 8 subjects in the overall analysis population (1.7% [8 of 464 subjects], 1.4 events per 100 person-year). One of these 11 events was serious. In 5 of 8 subjects, the events of sarcoidosis led to study discontinuation; all events occurred in patients with uveitis associated with sarcoidosis or patients with a history of sarcoidosis. No new onset of sarcoidosis was noted in clinical studies in patients with uveitis.

Adalimumab-induced exacerbation of the underlying disease (etiology) of uveitis may have resulted in the onset of sarcoidosis. However, because (i) the onset of sarcoidosis cannot be clearly explained by the mechanism of action of adalimumab and (ii) a causal relationship to adalimumab could not be ruled out for some cases of sarcoidosis reported in the post-marketing surveillance in Japan or in spontaneous reporting systems, the applicant intends to continue to investigate the safety of adalimumab in patients with uveitis associated with sarcoidosis.

PMDA's view:

The use of adalimumab may cause exacerbation of sarcoidosis, because (i) all adverse events of sarcoidosis occurred in subjects with sarcoidosis-associated uveitis in the clinical studies of adalimumab and (ii) adverse events of sarcoidosis occurred more frequently in the adalimumab group than in the placebo group. Therefore, physicians should be advised to carefully monitor patients with

sarcoidosis-associated uveitis on adalimumab for possible exacerbation of sarcoidosis. The risk of exacerbation of sarcoidosis should continue to be investigated in a post-marketing surveillance study and other studies.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of adalimumab:

Generally, oral steroids are the first-line therapy for non-infectious uveitis. Adalimumab is intended to be used in patients with non-infectious uveitis who have had an inadequate response to oral steroids and patients with non-infectious uveitis requiring high-dose oral steroids for treatment of active disease. The clinical studies of adalimumab [see Section "7.1 Phase III study" and Section "7.2 Phase III study"] has demonstrated the efficacy of adalimumab in these patient populations. In Japan, the use of immunosuppressive agents including cyclosporine is considered for patients with inadequate response to oral steroids. However, adalimumab can be effective irrespective of the use of immunosuppressive therapy, because a subgroup analysis of subjects with or without the use of immunosuppressive agents including cyclosporine showed similar results in the two subgroups; the hazard ratios for time to treatment failure [95% CI] in subjects with and without immunosuppressive therapy were 0.59 [0.33, 1.08] and 0.53 [0.37, 0.78], respectively, in Study M10-877 and 0.51 [0.27, 0.95] and 0.61 [0.40, 0.92], respectively, in Study M10-880. Not only these patients evaluated in clinical studies but also patients with highly active uveitis are inferred to receive adalimumab in combination with steroids in the early stage of treatment. Moreover, patients intolerant to steroids may receive adalimumab alone.

In Japan, the therapeutic strategy for uveitis associated with Behcet's disease differs from that for other types of uveitis. The former is divided into 2 approaches: post-remission treatment (which focuses on the prevention of ocular inflammation to maintain remission) and acute-phase treatment (which serves for the treatment of ocular inflammation in the acute phase). For the post-remission treatment, colchicine[11)] is used as the first-line drug, cyclosporine as the second-line drug, and infliximab (genetical recombination) for severe cases. For the acute-phase treatment, steroid injection or oral steroid is used for inflammation in the posterior segment of the eye (*J Jpn Ophthalomol Soc.* 2012;116:394-426). Study M10-877 included patients with active uveitis who experienced disease flares despite oral steroid therapy, and Study M10-880 included patients with inactive uveitis who had a history of disease flare during the tapering of oral steroids. Both studies suggested the efficacy of adalimumab in patients with uveitis associated with Behcet's disease. However, the clinical positioning of adalimumab is unclear because oral steroids are not listed in Japanese guidelines as therapeutic drugs for the post-remission treatment, and because the number of patients with Behcet's disease previously treated with colchicine was limited among those enrolled in the clinical studies of adalimumab. Nevertheless, adalimumab can be placed in the same position as infliximab (genetical recombination) with the same mechanism of action as adalimumab, when used in the post-remission treatment. For the acute-phase treatment, adalimumab can be used concomitantly with steroids in patients with inadequate response to steroids.

11) For colchicine, the indication of uveitis associated with Behcet's disease has not been approved in Japan.

PMDA's view:

The applicant's explanation is understandable. There would be a certain number of patients with active uveitis requiring treatment with adalimumab starting in the early stage or patients in whom use of oral steroids is inappropriate for safety reasons. However, no studies have assessed the efficacy and safety of adalimumab in these patient populations. Studies M10-877 and M10-880 included patients with uveitis who had an inadequate response to oral steroids or patients with steroid-dependent uveitis who required high-dose oral steroids to control disease activity [see Section "7.R.1.2 Subjects of Phase III studies"]; thus, the efficacy and safety of adalimumab were confirmed in patients with non-infectious uveitis who had an inadequate response to conventional therapies (i.e., oral steroids as the first-line therapy for non-infectious uveitis). Therefore, adalimumab is positioned as a therapeutic option for patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who have had an inadequate response to conventional therapies and who are at a risk of impaired visual acuity, including patients with highly active uveitis who have had an inadequate response to oral steroids and who are at a risk of impaired visual acuity and patients with steroid-dependent uveitis who require high-dose oral steroids to control disease activity.

The clinical positioning of adalimumab in the treatment of uveitis associated with Behcet's disease was discussed. While patients with inadequate response to oral steroids were eligible for enrollment in the clinical studies of adalimumab, oral steroids are not listed in the Japanese clinical practice guidelines for the post-remission treatment of uveitis associated with Behcet's disease. For this reason, no conclusions on the clinical positioning of adalimumab can be drawn from the results of the studies conducted. However, adalimumab involves the risk of serious infection and other conditions as with a similar drug, infliximab (genetical recombination). Adalimumab should therefore be used for post-remission treatment in patients who have had an inadequate response to conventional therapies including cyclosporine, as is the case with infliximab (genetical recombination). The positioning of adalimumab relative to colchicine, cyclosporine, and infliximab (genetical recombination) used in Japan will be discussed at academic conferences and on other occasions. In Study M10-877 in patients with active non-infectious uveitis, the loading dose of prednisone 60 mg/day was administered at Week 0 to control disease activity and the dose was tapered. Since this study was not designed to investigate the efficacy of adalimumab for the acute-phase treatment of inflammation, the usefulness of adalimumab in the acute-phase treatment cannot be discussed based on the results of this study. For this reason, in principle, adalimumab should be used for the post-remission treatment of uveitis associated with Behcet's disease.

7.R.5 Indication

The initially proposed indication is "non-infectious intermediate uveitis, posterior uveitis, or panuveitis."

PMDA considered that the initially proposed indication of adalimumab should be altered to "the following diseases in patients who have had an inadequate response to conventional therapies: Non-infectious intermediate uveitis, posterior uveitis, and panuveitis," in the light of the following points:

- Studies M10-877 and M10-880 have demonstrated the efficacy of adalimumab. The subgroup analyses by inflammation site (intermediate uveitis, posterior uveitis, or panuveitis) of uveitis and disease etiology have suggested the efficacy of adalimumab in all subgroups [see Section "7.R.2 Efficacy"].
- In view of its clinical positioning, adalimumab should be used only in patients with Behcet's disease-associated uveitis who have had an inadequate response to conventional therapies, as with infliximab (genetical recombination), and patients with other types of non-infectious uveitis who have had an adequate response to conventional therapy with oral steroids [see Section "7.R.4 Clinical positioning"].

A final decision regarding the indication of adalimumab will be made based on comments raised by expert adviser in the Expert Discussion.

7.R.6 Dosage and administration

The applicant's explanation about the rationale for the dosage and administration of adalimumab for non-infectious uveitis:

To treat non-infectious uveitis, ocular inflammation should be reduced at an early treatment stage, thereby preventing the onset of vision disorders or impaired visual function. Therefore, the loading dose of 80 mg of adalimumab at Week 0 was selected so that serum adalimumab concentrations promptly reach steady state. Adalimumab 40 mg every 2 weeks was selected as the subsequent dosage, which is the same as the maintenance regimen for the approved indications. There were no tendency toward large differences in serum TNF-α concentrations between patients with non-infectious uveitis and patients treated for the approved indications of adalimumab (see Table 17). Thus, the dosage regimen selected for Phase III studies in patients with non-infectious uveitis was 80 mg Week 0, followed by 40 mg every 2 weeks starting 1 week after the initial dose.

Table 17. Comparison of serum TNF-α concentrations for approved indications of adalimumab and for non-infectious uveitis

Indication	Serum TNF-α concentration	Reference
Non-infectious uveitis	27 to 70 pg/mL	Invest Ophthalmol Vis Sci 2006; 47: 1557-61, Curr Med Res Opin 2004; 20: 155-7, Am J Ophthalmol 2006; 142: 429-34, Ocul Immunol Inflamm 2004; 12: 53-8, Ophthalmic Res 2001; 33: 251-5, Mol Vis 2011; 17: 2003-10, Br J Ophthalmol 2004; 88: 412-6
Psoriasis vulgaris	19 to 26 pg/mL	J Biol Regul Homeost Agents 1997; 11: 115-8, Mediators Inflamm 2005; 2005: 273-9, Clin Exp Dermatol 2010; 35: 645-9
Rheumatoid arthritis	>40 pg/mL to >100 pg/mL	Arthritis Rheum 1988; 31: 1041-5, J Rheumatol 2001; 28: 1211-7, Ann Rheum Dis 2003; 62: 472-5, Ann Rheum Dis 1990; 49: 665-7, Ann Rheum Dis 2011; 70: 1208-15
Crohn's disease	29 pg/mL to 14 ng/mL	Med Glas (Zenica) 2013; 10: 211-6, Immunopharmacol Immunotoxicol 1992; 14: 451-61, Clin Chem 2001; 47: 1297-301
Ulcerative colitis	29 pg/mL to 9.46 ng/mL	

Studies M10-877 and M10-880 have demonstrated the efficacy of adalimumab. Also, Adalimumab can be expected to be effective regardless of uveitis inflammation site or etiology [see Section "7.R.2 Efficacy"]. No new safety concerns were noted in patients with non-infectious uveitis. On the basis of these findings and other data, the dosage and administration for non-infectious uveitis can be specified by the following statement: "The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 80 mg, followed by 40 mg once every 2 weeks starting 1 week after the initial dose. Adalimumab is administered by subcutaneous injection."

PMDA's view:
The applicant's explanation is acceptable. The proposed dosage and administration (an initial dose of adalimumab 80 mg administered by subcutaneous injection, followed by s40 mg every 2 weeks starting 1 week after the initial dose) can be used.

7.R.7 Self-administration

PMDA asked the applicant to explain the efficacy and safety of self-administration of adalimumab in the treatment of non-infectious uveitis.

The applicant's explanation:
The efficacy results in subjects to whom adalimumab was administered by themselves (subjects with self-administration) were compared with those in subjects to whom adalimumab was not administered by themselves (subjects without self-administration) in the Japanese subgroup of Studies M10-877 and M10-880. The analysis showed no clear difference in time to treatment failure between the 2 subgroups (with or without self-administration) in the adalimumab group (see Table 18).

Table 18. Time to treatment failure in Japanese subjects with or without self-administration in Studies M10-877 and M10-880

	With or without self-administration	Time to treatment failure in each subject in adalimumab group (days)									
Study M10-877	With self-administration (2 subjects)	70	140								
	Without self-administration (6 subjects)	41	43	43	77	147	147				
Study M10-880	With self-administration (6 subjects)	73	82	85	247	308	476 [a)]				
	Without self-administration (10 subjects)	36	50	57	66	78	92	252 [b)]	274 [a)]	280	567 [c)]

a) The study ended without treatment failure.
b) The study was discontinued due to adverse events.
c) Completed 80 weeks of treatment without treatment failure.

Table 19 shows the results of the pooled analysis of Studies M10-877 and M10-880. The analysis did not show a trend toward a higher incidence of adverse events in subjects with self-administration than in subjects without self-administration. No adverse events associated with injection were reported by subjects to whom adalimumab was administered by themselves.

Table 19. Summary of adverse events in Japanese subjects with or without self-injection

	With self-administration of adalimumab (N = 22)	Without self-administration of adalimumab (N = 24)
Adverse events	19 (86.4)	23 (95.8)
Adverse reactions	5 (22.7)	8 (33.3)
Serious adverse events	5 (22.7)	8 (33.3)
Adverse events leading to discontinuation	1 (4.5)	3 (12.5)
Infections	10 (45.5)	14 (58.3)
Serious infections	0	2 (8.3)
Injection site reactions	2 (9.1)	1 (4.2)
Allergic reactions	0	2 (8.3)

n (%)

PMDA's view:

Self-administration of adalimumab has brought to light no efficacy or safety concerns so far. Any particular efficacy or safety problem is unlikely to arise in association with self-administration by patients with non-infectious uveitis if adequate instruction regarding self-administration is provided through materials and other tools, as with approved indication. However, since clinical experience with self-administration is limited in Japan, issues related to self-administration should continue to be carefully investigated in a post-marketing surveillance study.

7.R.8 Post-marketing safety measures, etc.

Since no treatment guidelines have been established for non-infectious uveitis in Japan, clinical guidelines for the use of adalimumab (which specify physicians and institutions qualified for the use of adalimumab) should be provided to healthcare professionals. This is also important to avoid the injudicious use of adalimumab. PMDA therefore asked the applicant to explain the plan for developing clinical guidelines for the use of adalimumab.

The applicant's explanation:

To ensure the proper use of adalimumab, its use should be limited to physicians with sufficient knowledge of the use of adalimumab and with sufficient experience in treating non-infectious uveitis and to institutions which allow for collaboration with other specialist physicians, especially in the department of internal medicine, in case of serious infection. Currently, the Japanese Ocular Inflammation Society (JOIS) is developing "clinical guidelines for use of TNF-α inhibitors in the treatment of non-infectious uveitis and safety manuals (2016) (tentative title)." Collaboration with physicians in the department of internal medicine (respiratory medicine, internal medicine for connective tissue diseases or infectious diseases) is essential in case of serious infection, a safety risk associated with adalimumab. The clinical guidelines specify that collaboration with specialist physicians in other departments including those of internal medicine is a prerequisite to respond to the adverse reactions. In light of this point, the applicant plans to take the following safety measures, consisting mainly of strict compliance with the clinical guidelines for use of TNF-α inhibitors developed by the JOIS.

(a) Relevant information will be communicated, by direct mails or through medical representatives, to institutions to which adalimumab is supplied or will be supplied, so as to advise that adalimumab should be used only by qualified physicians in qualified institutions.

(b) Information on the proper use of adalimumab will be provided to institutions and physicians that are considered to fulfill the requirements of the guidelines.

(c) The institutions fulfilling the requirements of the guidelines will be announced on the applicant's website. Moreover, the applicant will, from time to time, update relevant information, such as the status of a post-marketing surveillance study planned in patients with non-infectious uveitis and adverse reactions reported in the surveillance study, on its website for healthcare professionals. If infections and other events arising after the use of adalimumab are difficult to evaluate, objective advice will be sought from external specialists in infectious diseases. The obtained advice will be reflected in the evaluation of such events.

PMDA's view:

To ensure the proper use of adalimumab, clinical guidelines for the use of TNF-α inhibitors should be developed based on the therapeutic strategy agreed by relevant academic societies and should be disseminated to healthcare professionals. Moreover, adalimumab must be used by physicians, who are familiar with the treatment of non-infectious uveitis and who have sufficient knowledge of adalimumab, in collaboration with specialist physicians in the departments of internal medicine that allow safety evaluations and treatment of adverse reactions to adalimumab. Accordingly, the applicant should provide adequate advice and information to physicians who intend to use adalimumab in patients with non-infectious uveitis.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed inappropriate practice. Specifically, the sponsor allowed monitors to change or correct the entries on some pages of case report forms that had been completed by investigators or other personnel in the electronic data-processing system used for the studies. Although the above finding requiring corrective action was noted, it had no impact on the data integrity or the evaluation of overall study results. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-2) were subjected to an on-site GCP inspection, in accordance with the provisions in the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. Based on this inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that adalimumab has efficacy in the treatment of patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who have had an inadequate response to conventional therapies, and that adalimumab has acceptable safety in view of its benefits. Humira (adalimumab) has clinical significance because it offers a new therapeutic option for uveitis. The occurrence of adverse events including serious infection associated with long-term use of adalimumab should continue to be investigated in a post-marketing surveillance study.

PMDA has concluded that Humira (adalimumab) may be approved if the product is not considered to have any particular problems based on comments raised in the Expert Discussion.

Review Report (2)

August 30, 2016

Product Submitted for Approval

Brand Name	(a) Humira 40 mg for S.C Injection Syringe 0.8 mL
	(b) Humira 40 mg for S.C. Injection Syringe 0.4 mL
	(c) Humira 80 mg for S.C. Injection Syringe 0.8 mL
Non-proprietary Name	Adalimumab (Genetical Recombination)
Applicant	AbbVie GK
Date of Application	(a) October 29, 2015
	(b), (c) July 22, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

The high-concentration formulations (Humira 40 mg for S.C. Injection Syringe 0.4 mL and Humira 80 mg for S.C. Injection Syringe 0.8 mL) were approved in June 2016 based on the results of studies assessing bioequivalence with Humira 40 mg for S.C. Injection Syringe 0.8 mL (the drug product initially proposed in the present application). For this reason, the partial change application for addition of indication of non-infectious intermediate uveitis, posterior uveitis, or panuveitis was filed for these high-concentration formulations based on the results of clinical studies of the initially proposed drug product in patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

1.1 Efficacy, safety, indication, and dosage and administration

In the Expert Discussion, expert advisors supported PMDA's conclusion regarding the efficacy, safety, indication, and dosage and administration of adalimumab presented in Review Report (1) while raising the following comments.

- Adalimumab is an important therapeutic option for patients with refractory intermediate uveitis, posterior uveitis, or panuveitis who have had an inadequate response to oral steroids, and its medical need is considered high. However, due attention should be paid to the risk of adverse events such as serious infection and malignant tumors in patients treated with adalimumab. The applicant should provide adequate advice and information to healthcare professionals so as to avoid the injudicious use of adalimumab (including high-concentration formulations).

1.2 Risk management plan (draft)

Based on the review presented in Section "7.R.8 Post-marketing safety measures, etc." in Review Report (1), the current risk management plan (draft) for adalimumab (including high-concentration formulations) was examined. PMDA has concluded that the risk management plan should include the safety and efficacy specifications shown in Table 20 and that the applicant should conduct the additional pharmacovigilance activities and risk-minimizing activities shown in Table 21.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specificatioin		
Important identified risks	Important potential risks	Important missing information
• Serious infection • Reactivation of hepatitis B • Tuberculosis • Demyelination disease • Lupus-like syndrome • Serious allergic reaction • Interstitial pneumonia • Serious blood disorder • Fulminant hepatitis, hepatic dysfunction, jaundice, liver failure	• Malignant tumor • Exacerbation and new onset of psoriasis • Exacerbation of sarcoidosis • Narrowing of colon lumen (for Crohn's disease) • Immunogenicity	Not applicable
Efficacy specification		
• Long-term efficacy in patients with non-infectious uveitis • Long-term efficacy in patients with Crohn's disease • Efficacy in patients with ankylosing spondylitis • Efficacy in patients with active polyarticular juvenile idiopathic arthritis • Efficacy in patients with intestinal Behcet's disease • Long-term efficacy in patients with ulcerative colitis		

Table 21. Summary of additional pharmacovigilance activities and risk-minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk-minimizing activities
• Early post-marketing phase vigilance (indication, non-infectious uveitis) • Specified use-results survey (on long-term use of adalimumab in patients with non-infectious uveitis) • Specified use-results survey (on the safety and efficacy of adalimumab in combination with high-dose methotrexate in patients with rheumatoid arthritis) • Specified use-results survey (on long-term use of adalimumab in patients with Crohn's disease) • Specified use-results survey (all-case surveillance in patients with ankylosing spondylitis) • Specified use-results survey (all-case surveillance in patients with active polyarticular juvenile idiopathic arthritis) • Specified use-results survey (all-case surveillance in patients with intestinal Behcet's disease) • Specified use-results survey (long-term survey in patients with ulcerative colitis) • Specified use-results survey (Work Productivity and Activity Impairment survey in patients with psoriatic arthritis engaging in wage labor)	• Early post-marketing phase vigilance (indication, non-infectious uveitis) • Preparation and provision of materials (guide to proper use) for healthcare professionals • Preparation and provision of patient education materials related to self-administration • Ensuring information provision before delivery of the product

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

The applicant's explanation:

The applicant plans to assess the safety and efficacy of adalimumab in clinical use by conducting a specified use-results survey with 52-week observation period in a total of 250 patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who have had an inadequate response

to conventional therapies (for the safety analysis population). The priority survey items are serious infection, reactivation of hepatitis B, tuberculosis, demyelination disease, lupus-like syndrome, serious allergic reaction, interstitial pneumonia, serious blood disorder, fulminant hepatitis, hepatic dysfunction, jaundice, and liver failure. To further assess the long-term safety of adalimumab, patients included in the survey will be followed for malignant tumor after the observation period, and the follow-up will be continued up to 2 years after the start of treatment (see Table 22).

Table 22. Outline of specified use-results survey plan (draft)

Objective	To confirm the safety and efficacy of adalimumab in clinical use
Survey method	Central registry system
Population	Patients with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who have had an inadequate response to conventional therapies
Observation period	52 weeks after the start of treatment (follow-up is continued up to 2 years after the start of treatment)
Planned sample size	250 patients (for safety analysis population)
Main survey items	• Priority survey items: serious infection, reactivation of hepatitis B, tuberculosis, demyelination disease, lupus-like syndrome, serious allergic reaction, interstitial pneumonia, serious blood disorder, fulminant hepatitis, hepatic dysfunction, jaundice, and liver failure • Patient characteristics (duration of disease, severity, etiology, history, etc.) • Previous therapy • Use of adalimumab • Concomitant therapy • Laboratory tests • Adverse events (including malignant tumor) • Efficacy

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication as well as the dosage and administration shown below. The present application has been filed for the approval of a drug with new indication and dosage. The re-examination period should be 4 years for the proposed indication and dosage and administration.

Indication

Rheumatoid arthritis (including treatments to prevent structural damage of joints)

The following diseases in patients who have had an inadequate response to conventional therapies:

Psoriasis vulgaris and psoriatic arthritis

Ankylosing spondylitis

Active polyarticular juvenile idiopathic arthritis

Intestinal Behcet's disease

Non-infectious intermediate uveitis, posterior uveitis, or panuveitis

Remission induction and maintenance therapies for moderate to severe active Crohn's disease (only in patients who have had an inadequate response to conventional therapies)

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

(Underline denotes additions.)

Dosage and Administration

Rheumatoid arthritis

The usual adult dosage of Adalimumab (Genetical Recombination) is 40 mg administered once every 2 weeks by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Psoriasis vulgaris and psoriatic arthritis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 80 mg, followed by 40 mg once every 2 weeks. Adalimumab is administered by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Ankylosing spondylitis

The usual adult dosage of Adalimumab (Genetical Recombination) is 40 mg administered once every 2 weeks by subcutaneous injection. If an adequate response is not achieved, the dose can be increased up to 80 mg per administration.

Active polyarticular juvenile idiopathic arthritis

The usual dosage of Adalimumab (Genetical Recombination) is as follows:

- patients weighing ≥15 kg and <30 kg: 20 mg once every 2 weeks
- patients weighing ≥30 kg: 40 mg once every 2 weeks

Adalimumab is administered by subcutaneous injection.

Intestinal Behcet's disease

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

Non-infectious intermediate uveitis, posterior uveitis, or panuveitis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 80 mg, followed by 40 mg 1 week later, and then 40 mg once every 2 weeks starting 3 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

Crohn's disease

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection. If an decreased response is noted, the dose can be increased up to 80 mg per administration.[3)]

Ulcerative colitis

The usual adult dosage of Adalimumab (Genetical Recombination) is an initial dose of 160 mg, followed by 80 mg 2 weeks later, and then 40 mg once every 2 weeks starting 4 weeks after the initial dose. Adalimumab is administered by subcutaneous injection.

(Underline denotes additions.)

Conditions of Approval

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