

Report on the Deliberation Results

December 4, 2008

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

[Brand name] Xolair for subcutaneous injection for 150 mg administration
[Non-proprietary name] Omalizumab (Genetical Recombination) (JAN*)
[Applicant] Novartis Pharma K.K.
[Date of application] May 31, 2006

[Results of deliberation]

In the meeting held on November 28, 2008, the First Committee on New Drugs concluded that the brand name should be changed from “Xolair for subcutaneous injection for 150 mg administration” to “Xolair for subcutaneous injection” and then the result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

With a view to preventing medical accidents, it was decided that “Water for Injection” should not be attached.

**Japanese Accepted Name (modified INN)*

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

Report on the Deliberation Results

November 6, 2008

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

[Brand name] Xolair for subcutaneous injection 150 mg
[Non-proprietary name] Omalizumab (Genetical Recombination)
[Applicant] Novartis Pharma K.K.
[Date of application] May 31, 2006

[Results of deliberation]

In the meeting held on October 27, 2008, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

With a view to preventing medical accidents, it was decided that the brand name should be changed from “Xolair for subcutaneous injection 150 mg” to “Xolair for subcutaneous injection for 150 mg administration.”

Review Report

October 17, 2008

Pharmaceuticals and Medical Devices Agency

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

[Brand name] Xolair for subcutaneous injection 150 mg
[Non-proprietary name] Omalizumab (Genetical Recombination)
[Name of applicant] Novartis Pharma K.K.
[Date of application] May 31, 2006
[Dosage form/Strength] 202.5 mg of Omalizumab (Genetical Recombination) as lyophilized powder for injection in a vial
[Application classification] Prescription drug (1) Drug with a new active ingredient

[Chemical structure]

Molecular weight: approximately 149,000

Structural formula: See the figure on next page.

Chemical name or active ingredient:

Glycoprotein (molecular weight, ca. 149,000) consisting of two molecules of light chains and two molecules of heavy chains produced in Chinese hamster ovary cells transfected with DNA encoding a light chain consisting of 218 amino acid residues ($C_{1048}H_{1609}N_{278}O_{350}S_6$; molecular weight, 23895.03) and a heavy chain consisting of 451 amino acid residues ($C_{2204}H_{3389}N_{588}O_{673}S_{15}$; molecular weight, 49372.00) derived from humanized mouse anti-human IgE monoclonal antibody, which consists of a complementarity-determining region derived from mouse anti-human IgE monoclonal antibody and a constant region and a framework region derived from human IgG1.

[Items warranting special mention] None

[Reviewing office] Office of New Drug IV

Figure. Amino acid sequence of Omalizumab (Genetical Recombination)

Light chain

| | | |
|--|-----|-----|
| | 10 | 20 |
| Asp-Ile-Gln-Leu-Thr-Gln-Ser-Pro-Ser-Ser-Leu-Ser-Ala-Ser-Val-Gly-Asp-Arg-Val-Thr- | 30 | 40 |
| Ile-Thr-Cys-Arg-Ala-Ser-Gln-Ser-Val-Asp-Tyr-Asp-Gly-Asp-Ser-Tyr-Met-Asn-Trp-Tyr- | 50 | 60 |
| Gln-Gln-Lys-Pro-Gly-Lys-Ala-Pro-Lys-Leu-Leu-Ile-Tyr-Ala-Ala-Ser-Tyr-Leu-Glu-Ser- | 70 | 80 |
| Gly-Val-Pro-Ser-Arg-Phe-Ser-Gly-Ser-Gly-Ser-Gly-Thr-Asp-Phe-Thr-Leu-Thr-Ile-Ser- | 90 | 100 |
| Ser-Leu-Gln-Pro-Glu-Asp-Phe-Ala-Thr-Tyr-Tyr-Cys-Gln-Gln-Ser-His-Glu-Asp-Pro-Tyr- | 110 | 120 |
| Thr-Phe-Gly-Gln-Gly-Thr-Lys-Val-Glu-Ile-Lys-Arg-Thr-Val-Ala-Ala-Pro-Ser-Val-Phe- | 130 | 140 |
| Ile-Phe-Pro-Pro-Ser-Asp-Glu-Gln-Leu-Lys-Ser-Gly-Thr-Ala-Ser-Val-Val-Cys-Leu-Leu- | 150 | 160 |
| Asn-Asn-Phe-Tyr-Pro-Arg-Glu-Ala-Lys-Val-Gln-Trp-Lys-Val-Asp-Asn-Ala-Leu-Gln-Ser- | 170 | 180 |
| Gly-Asn-Ser-Gln-Glu-Ser-Val-Thr-Glu-Gln-Asp-Ser-Lys-Asp-Ser-Thr-Tyr-Ser-Leu-Ser- | 190 | 200 |
| Ser-Thr-Leu-Thr-Leu-Ser-Lys-Ala-Asp-Tyr-Glu-Lys-His-Lys-Val-Tyr-Ala-Cys-Glu-Val- | 210 | 218 |
| Thr-His-Gln-Gly-Leu-Ser-Ser-Pro-Val-Thr-Lys-Ser-Phe-Asn-Arg-Gly-Glu-Cys | | |

Heavy chain

| | | |
|--|------|-----|
| | 10 | 20 |
| Glu-Val-Gln-Leu-Val-Glu-Ser-Gly-Gly-Gly-Leu-Val-Gln-Pro-Gly-Gly-Ser-Leu-Arg-Leu- | 30 | 40 |
| Ser-Cys-Ala-Val-Ser-Gly-Tyr-Ser-Ile-Thr-Ser-Gly-Tyr-Ser-Trp-Asn-Trp-Ile-Arg-Gln- | 50 | 60 |
| Ala-Pro-Gly-Lys-Gly-Leu-Glu-Trp-Val-Ala-Ser-Ile-Thr-Tyr-Asp-Gly-Ser-Thr-Asn-Tyr- | 70 | 80 |
| Asn-Pro-Ser-Val-Lys-Gly-Arg-Ile-Thr-Ile-Ser-Arg-Asp-Asp-Ser-Lys-Asn-Thr-Phe-Tyr- | 90 | 100 |
| Leu-Gln-Met-Asn-Ser-Leu-Arg-Ala-Glu-Asp-Thr-Ala-Val-Tyr-Tyr-Cys-Ala-Arg-Gly-Ser- | 110 | 120 |
| His-Tyr-Phe-Gly-His-Trp-His-Phe-Ala-Val-Trp-Gly-Gln-Gly-Thr-Leu-Val-Thr-Val-Ser- | 130 | 140 |
| Ser-Ala-Ser-Thr-Lys-Gly-Pro-Ser-Val-Phe-Pro-Leu-Ala-Pro-Ser-Ser-Lys-Ser-Thr-Ser- | 150 | 160 |
| Gly-Gly-Thr-Ala-Ala-Leu-Gly-Cys-Leu-Val-Lys-Asp-Tyr-Phe-Pro-Glu-Pro-Val-Thr-Val- | 170 | 180 |
| Ser-Trp-Asn-Ser-Gly-Ala-Leu-Thr-Ser-Gly-Val-His-Thr-Phe-Pro-Ala-Val-Leu-Gln-Ser- | 190 | 200 |
| Ser-Gly-Leu-Tyr-Ser-Leu-Ser-Ser-Val-Val-Thr-Val-Pro-Ser-Ser-Ser-Leu-Gly-Thr-Gln- | 210 | 220 |
| Thr-Tyr-Ile-Cys-Asn-Val-Asn-His-Lys-Pro-Ser-Asn-Thr-Lys-Val-Asp-Lys-Lys-Val-Glu- | 230* | 240 |
| Pro-Lys-Ser-Cys-Asp-Lys-Thr-His-Thr-Cys-Pro-Pro-Cys-Pro-Ala-Pro-Glu-Leu-Leu-Gly- | 250 | 260 |
| Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr- | 270 | 280 |
| Pro-Glu-Val-Thr-Cys-Val-Val-Val-Asp-Val-Ser-His-Glu-Asp-Pro-Glu-Val-Lys-Phe-Asn- | 290 | 300 |
| Trp-Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-Glu-Glu-Gln-Tyr- | 310 | 320 |
| Asn-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly- | 330 | 340 |
| Lys-Glu-Tyr-Lys-Cys-Lys-Val-Ser-Asn-Lys-Ala-Leu-Pro-Ala-Pro-Ile-Glu-Lys-Thr-Ile- | 350 | 360 |
| Ser-Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-Pro-Ser-Arg-Glu- | 370 | 380 |
| Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp- | 390 | 400 |
| Ile-Ala-Val-Glu-Trp-Glu-Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro- | 410 | 420 |
| Val-Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Lys-Leu-Thr-Val-Asp-Lys-Ser-Arg- | 430 | 440 |
| Trp-Gln-Gln-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-Met-His-Glu-Ala-Leu-His-Asn-His-Tyr- | 450 | |
| Thr-Gln-Lys-Ser-Leu-Ser-Leu-Ser-Pro-Gly-Lys | | |

Review Results

October 17, 2008

[Brand name] Xolair for subcutaneous injection 150 mg
[Non-proprietary name] Omalizumab (Genetical Recombination)
[Name of applicant] Novartis Pharma K.K.
[Date of application] May 31, 2006

[Results of review]

The submitted data have demonstrated the efficacy and safety of the product in patients with bronchial asthma.

The results from Japanese clinical studies etc. have shown a certain level of clinical efficacy.

Regarding safety, since overseas post-marketing safety data etc. have raised a concern about the development of anaphylaxis including delayed reactions, patients' symptoms should be carefully observed after the administration of the product and patients should also be informed of the signs and symptoms of anaphylaxis. In addition, it is necessary to further investigate the safety of its long-term use, including the occurrence of malignancies, through post-marketing surveillance.

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

[Indication]

Bronchial asthma (only for refractory patients whose asthma symptoms are not controlled by conventional therapies)

[Dosage and administration]

The usual adult dosage is 75 to 375 mg of Omalizumab (Genetical Recombination) administered by subcutaneous injection every 2 or 4 weeks. Doses and dosing frequency are determined by serum total IgE level, measured before the start of treatment, and body weight, according to the dosing charts below.

Dosing charts (Dose for each administration)

Administration Every 4 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | |
|--|------------------|---------|---------|---------|---------|---------|---|-----------|--|
| | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| ≥ 30-100 | 75 mg | 150 mg | 150 mg | 150 mg | 150 mg | 150 mg | 300 mg | 300 mg | |
| > 100-200 | 150 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | Administration Every 2 Weeks See the table below | | |
| > 200-300 | 225 mg | 300 mg | 300 mg | | | | | | |
| > 300-400 | 300 mg | | | | | | | | |
| > 400-500 | | | | | | | | | |
| > 500-600 | | | | | | | | | |
| > 600-700 | | | | | | | | | |

Administration Every 2 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | |
|--|------------------------------|---------|---------|---------|---------|---------|-------------------|-----------|--|
| | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| ≥ 30-100 | Administration Every 4 Weeks | | | | | | | | |
| > 100-200 | See the above table | | | | | | 225 mg | 300 mg | |
| > 200-300 | | | | 225 mg | 225 mg | 225 mg | 300 mg | 375 mg | |
| > 300-400 | 225 mg | | 225 mg | 225 mg | 300 mg | 300 mg | Do not administer | | |
| > 400-500 | 225 mg | 225 mg | 300 mg | 300 mg | 375 mg | 375 mg | | | |
| > 500-600 | 225 mg | 300 mg | 300 mg | 375 mg | | | | | |
| > 600-700 | 225 mg | 300 mg | 375 mg | | | | | | |

Dosing in a given cell of the dosing charts has been calculated to provide the recommended clinical dose of ≥ 0.008 mg/kg/[IU/mL] (every 2 weeks by subcutaneous injection) or ≥ 0.016 mg/kg/[IU/mL] (every 4 weeks by subcutaneous injection) of Omalizumab.

Review Report (1)

September 12, 2008

I. Product Submitted for Registration

[Brand name] Xolair for subcutaneous injection 150 mg
[Non-proprietary name] Omalizumab (Genetical Recombination)
[Name of applicant] Novartis Pharma K.K.
[Date of application] May 31, 2006
[Dosage form/Strength] 202.5 mg of Omalizumab (Genetical Recombination) as lyophilized powder for injection in a vial
[Proposed indication] Bronchial asthma (only for patients who respond inadequately to conventional therapies)
[Proposed dosage and administration]
The usual adult dosage is 150 to 375 mg of Omalizumab (Genetical Recombination) administered by subcutaneous injection every 2 or 4 weeks. Doses and dosing frequency are determined by serum total IgE level, measured before the start of treatment, and body weight.

II. Summary of the Submitted Data and the Outline of Review

The data submitted in this application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

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

The active ingredient of the product, Omalizumab (Genetical Recombination) is a humanized mouse anti-human IgE monoclonal antibody generated by Genentech, Inc. (the US). Omalizumab is considered to exhibit its pharmacological effects as follows: it binds to the Cε3 domain of free IgE in blood, preventing IgE from binding to inflammatory cells (mast cells, basophils, etc.), thus inhibiting the activation of inflammatory cells, the release of inflammatory mediators such as histamine and leukotriene, and the release of Th2 cytokines. The development of Omalizumab as a treatment for type I allergic diseases including allergic asthma and [REDACTED] was progressed.¹

In foreign countries, based on the results from double-blind, placebo-controlled, comparative studies in patients with moderate-to-severe persistent allergic asthma who are symptomatic despite daily treatment with medium- or high-dose inhaled corticosteroids and as-needed or regular use of short-acting inhaled β₂-agonists (Studies 008 and 009), an application for the approval of Omalizumab

¹ Omalizumab is unapproved for [REDACTED] both in and outside Japan as of [REDACTED] 20[REDACTED].

was filed in Australia, the US, and Europe in [REDACTED] 20[REDACTED]. Omalizumab was approved for “the management of adult and adolescent patients with moderate allergic asthma, who have been treated with inhaled steroids, and who have elevated serum IgE levels” in Australia in June 2002 and for “decreasing the incidence of asthma exacerbations in adults and adolescents (12 years of age and above) with moderate to severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids” in the US in June 2003. On the other hand, in Europe, the application was withdrawn in [REDACTED] 20[REDACTED] following discussions with the regulatory authority, because it was concluded that taking account of the advances in standard therapy for asthma due to the widespread use of long-acting inhaled β_2 -agonists, the patient population in the confirmatory studies was not appropriate for treatment with Omalizumab, which should be indicated for a patient population at high risk of asthma death who responds inadequately to the best available therapy. Then, based on the results from an additional clinical study (Study 2306), an application for the approval of Omalizumab was re-submitted in [REDACTED] 20[REDACTED] and the drug product was approved as “add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and older) with severe persistent allergic asthma who have reduced lung function ($FEV_1 < 80\%$ of the predicted normal value) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented asthma exacerbations despite high-dose inhaled corticosteroids, plus a long-acting inhaled β_2 -agonist” in October 2005. As of August 2008, Omalizumab has been approved as a treatment for allergic asthma in 70 countries.

In Japan, a clinical study began in [REDACTED] 19[REDACTED] and initially, a bridging study (Study 1301) designed to extrapolate [REDACTED], [REDACTED], was undertaken based on the bridging concept, but the study was prematurely terminated because it was unsuitable for the Japanese medical practice. In February 2003, a double-blind, placebo-controlled, comparative study in patients with bronchial asthma who respond inadequately to conventional therapies (Study 1304), etc. started to be conducted. The applicant claims that the efficacy and safety of Omalizumab have now been confirmed, and has filed a marketing application for Omalizumab based on the clinical data package from Japanese studies.

2. Data relating to quality

2.A Summary of the submitted data

Omalizumab (Genetical Recombination) is a glycoprotein (molecular weight, ca. 149,000) consisting of two molecules of light chains and two molecules of heavy chains produced in Chinese hamster ovary cells transfected with DNA encoding a light chain consisting of 218 amino acid residues ($C_{1048}H_{1609}N_{278}O_{350}S_6$; molecular weight, 23895.03) and a heavy chain consisting of 451 amino acid residues ($C_{2204}H_{3389}N_{588}O_{673}S_{15}$; molecular weight, 49372.00) derived from humanized mouse anti-human IgE monoclonal antibody, which consists of a complementarity-determining region derived from mouse anti-human IgE monoclonal antibody and a constant region and a framework region derived from human IgG1.

2.A.(1) Manufacturing process for the drug substance

2.A.(1).1 Establishment of cell banking system

In order to prepare a gene encoding Omalizumab, hybridomas were produced by fusing spleen cells from BALB/c mice, which were immunized with human IgE with λ light chains secreted by the U266 multiple myeloma cell line, with the mouse myeloma cell line. Among several hybridoma cell lines producing anti-human IgE mouse monoclonal antibodies that bind to human IgE and do not bind to human IgG, a hybridoma producing an anti-human IgE mouse monoclonal antibody (MaE11) was selected because it does not bind to human IgE bound to Fc ϵ RI α or human IgE bound to Fc ϵ RII but inhibits the binding of human IgE to Fc ϵ RI α and Fc ϵ RII chains, and gives a negative histamine release test. MaE11 was humanized by Carter et al.'s method (Carter P et al., *Proc Natl Acad Sci USA*. 1992;89:4285-4289) (Presta LC et al., *J Immunol*. 1993;151:2623-2632) and its framework amino acids that affect the conformation of the complementarity determining regions (CDRs) were modified to produce the gene of Omalizumab, a humanized MaE11 that provides for IgE binding comparable to that of MaE11.

In order to generate the expression construct, the DNA encoding [REDACTED] was integrated into pSV16B5 Δ d vector in which the human cytomegalovirus promoter of the pCIS2 vector (Gorman et al., *DNA and Protein Engineering Techniques*. 1990;2:3-10) was replaced with SV40 transcriptional element. Then, Omalizumab expression vector pSVIE25 was constructed by inserting the DNA fragments containing the DNA encoding [REDACTED] and [REDACTED] transcriptional element for its expression.

The host cells, CHO-[REDACTED] cells were transfected with Omalizumab expression vector pSVIE25 by electroporation and selected in medium lacking glycine, hypoxanthine, and thymidine before a cell clone was selected based on the proliferative capacity and antibody production capacity in medium containing methotrexate. A master cell bank (MCB) was prepared from these cells and a working cell bank (WCB) was prepared from the MCB.

2.A.(1).2 Characterization and control of cell banks

Characterization studies and purity tests have been performed on the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL).

The MCB has been characterized by the identity of the cell line, restriction enzyme analysis, DNA copy number, analysis of transcribed mRNA, and nucleotide sequencing. Purity tests performed on the MCB include sterility test, mycoplasma testing, adventitious virus *in vitro* assay (inoculation into MRC-5, Vero, and CHO-K1 cells, observation of hemagglutination of chicken, guinea pig, and human red blood cells after inoculation), antibody production tests (mouse antibody production test, hamster antibody production test), *in vivo* assay to reveal latent viruses (inoculation into adult mice, guinea pigs, and suckling mice, observation of hemagglutination of guinea pig, chicken, and human red blood cells in the allantoic fluid of inoculated embryonated eggs, embryonic death after yolk-sac inoculation), reverse transcriptase activity assay, S⁺L⁻ assay, test for retroviruses by cocultivation (cocultivation

with human rhabdomyosarcoma cells [RD], mink lung cells [Mv1Lu], dog thymus cells [CF2Th], bat lung cells [TB1LU], and human lung carcinoma cells [A549]), transmission electron microscopy of cell pellets, and quantification of retrovirus particles. As a result, the MCB showed no detectable, bacterial, mycoplasma, or viral contamination within the scope of the tests performed.

The WCB has been characterized by the identity of the cell line and of the product. Purity tests performed on the WCB include sterility test, mycoplasma testing, adventitious virus *in vitro* assay (inoculation into MRC-5, Vero, CHO-K1, and 324K cells, observation of hemagglutination of chicken, guinea pig, and human red blood cells after inoculation), antibody production tests (mouse antibody production test, hamster antibody production test), *in vivo* assay to reveal latent viruses (inoculation into adult mice, guinea pigs, and suckling mice, observation of hemagglutination of guinea pig, chicken, and human red blood cells in the allantoic fluid of inoculated embryonated eggs, embryonic death after yolk-sac inoculation), and quantification of retrovirus particles. As a result, the WCB showed no detectable, bacterial, mycoplasma, or viral contamination within the scope of the tests performed.

CAL has been characterized by restriction enzyme analysis, DNA copy number, and analysis of transcribed mRNA. Purity tests performed on CAL include reverse transcriptase activity assay, S⁺L⁻ assay, and transmission electron microscopy of cell pellets. As a result, CAL showed no detectable viral contamination within the scope of the tests performed.

Because it is possible to prepare more than [REDACTED] ampoules of the WCB from the current MCB, there is no plan to prepare a new MCB. The MCB is stored also outside the facility in case of disasters. The stability of the MCB during storage is to be confirmed by measuring cell viability when an ampoule of the MCB is thawed.

When an additional WCB is prepared in the same manner as the current MCB or WCB, sterility test, mycoplasma testing, rodent parvovirus test using 324K cells, *in vivo* assay to reveal latent viruses, general virus screening, identity test of the cell line, measurement of the number of viable cells, and identity test of the product are to be performed to confirm that the newly prepared WCB meets the acceptance criteria. When an additional WCB is prepared in a different manner from the current WCB, in addition to the above-mentioned tests, [REDACTED] test for cell culture and quality tests of the product are to be performed to confirm that the cell proliferation, productivity, and characteristics of the new WCB are comparable to those of the current WCB. The stability of the WCB is to be assessed based on cell viability and proliferative capacity for vials thawed for production and those meeting the specifications are to be used for production.

2.A.(1).3 Manufacturing process

The manufacturing process for the drug substance is as shown below.

| Cell culture process | In-process control tests |
|--|------------------------------------|
| <ul style="list-style-type: none">■ Seed culture<ul style="list-style-type: none">· Selective medium containing methotrexate· pH ■, ■°C · Subcultivation every ■-■ days | |
| ↓ | |
| <ul style="list-style-type: none">■ ■ L bioreactor■ ■ L bioreactor■ ■ L bioreactor<ul style="list-style-type: none">· Non-selective medium· pH ■■■, ■°C · Duration, every ■-■ days | |
| ↓ | |
| <ul style="list-style-type: none">■ 13500 L bioreactor<ul style="list-style-type: none">· Production medium (non-selective medium)· pH ■■■, ■°C · Duration, ■-■ days· When PCV is about ■% or up to ■ days later· pH ■■■, ■°C · Duration, ■ hours· Further adjustment of the pH to ■· Total culture duration, ■-■ days | Rodent parvovirus PCR (■th day) |
| ↓ | |
| <ul style="list-style-type: none">■ 13500 L pre-harvest stage | Rodent parvovirus PCR Bioburden |
| ↓ | |
| <ul style="list-style-type: none">■ Harvesting by centrifugation | |
| ↓ | |
| <ul style="list-style-type: none">■ Depth filtration | |
| ↓ | |
| <ul style="list-style-type: none">■ Sterile filtration | |
| ↓ | |
| <ul style="list-style-type: none">■ Harvested cell culture fluid<ul style="list-style-type: none">· Crude Omalizumab separated from cells may be held at ■°C to ■°C for up to ■ days | Bioburden ■ measurement |

| Purification process | In-process control tests |
|--|---|
| <ul style="list-style-type: none"> ■ [REDACTED] affinity chromatography | <ul style="list-style-type: none"> Bioburden pH |
| ↓ | |
| <ul style="list-style-type: none"> ■ [REDACTED] ion exchange chromatography <ul style="list-style-type: none"> · May be held [REDACTED] for up to [REDACTED] days or at [REDACTED]°C to [REDACTED]°C for up to [REDACTED] days | <ul style="list-style-type: none"> Bioburden |
| ↓ | |
| <ul style="list-style-type: none"> ■ [REDACTED] ion exchange chromatography <ul style="list-style-type: none"> · May be held [REDACTED] for up to [REDACTED] days or at [REDACTED]°C to [REDACTED]°C for up to [REDACTED] days | <ul style="list-style-type: none"> Bioburden Bacterial endotoxins |
| ↓ | |
| <ul style="list-style-type: none"> ■ Ultrafiltration of [REDACTED] pool (UF/DF) <ul style="list-style-type: none"> · Formulated in [REDACTED] mmol/L histidine, [REDACTED] mmol/L sucrose, and [REDACTED]% polysorbate 20 at a pH of about [REDACTED] | <ul style="list-style-type: none"> Bioburden |
| ↓ | |
| <ul style="list-style-type: none"> ■ Addition of [REDACTED] | <ul style="list-style-type: none"> [REDACTED] assay |
| ↓ | |
| <ul style="list-style-type: none"> ■ Addition of [REDACTED] | <ul style="list-style-type: none"> Bioburden Bacterial endotoxins Host cell proteins |
| ↓ | |
| <ul style="list-style-type: none"> ■ Sterile filtration and storage of bulk <ul style="list-style-type: none"> · Filled into 120 L stainless steel tanks and stored at below -20°C | |

Although the drug substance is manufactured at Novartis Pharma's [REDACTED] facility, process validation was performed by Genentech which initially manufactured Omalizumab. Novartis Pharma also performed process validation and as a result, the Novartis Pharma and Genentech processes were found to be comparable.

In the cell culture process at Genentech, the mean cumulative cell growth, cell viability in pre-harvest cultures, and Omalizumab yields and specific productivity were not dependent on cell age (up to [REDACTED] days from the MCB thaw) and had no effect on the properties of the obtained Omalizumab. Because a series of cell cultures studied took [REDACTED] to [REDACTED] hours, when cells within [REDACTED] days after the MCB thaw are cultured for up to [REDACTED] to [REDACTED] days, consistent production of Omalizumab should be possible.

It has been confirmed that host cell DNA and host cell proteins and process-related impurities, i.e. methotrexate, recombinant insulin, gentamicin, Pluronic F-68, Tris base, and [REDACTED], are adequately removed with good reproducibility in the purification process. The purification process steps have been designed to be done sequentially, and fluid at each step of purification can be held until the next step under the conditions established based on the results of stability studies. The yield at each purification step was measured for 3 lots, which has been determined to be consistent. [REDACTED] affinity chromatography column, [REDACTED] ion exchange chromatography column, and [REDACTED] ion exchange chromatography column, which are used in the purification process, have been shown to be capable of removing impurities and also give good recovery of Omalizumab for at least [REDACTED], [REDACTED], and [REDACTED].

█ cycles, respectively. Furthermore, the established cleaning procedures for the columns and membrane filters have been confirmed to reduce carryovers effectively.

The cell culture process, removal of impurities (host cell proteins, host cell DNA, █) in the purification process, and the recovery rate of Omalizumab at Novartis Pharma have been confirmed to be comparable to those at Genentech. █ chromatographic fillers were investigated and an alternative has been confirmed to be comparable to Genentech’s one. Moreover, Novartis Pharma changed chromatographic █ from the one used at Genentech, but this change has been confirmed to unaffected the purification process.

2.A.(1).4 Adventitious agents safety evaluation

The raw materials of biological origin used in the manufacturing process are recombinant human insulin and hydrolyzed peptone. Hydrolyzed peptone used in the cell culture process is derived from porcine stomach sourced from the US and high-temperature, short-time sterilization is performed before its use to inactivate viruses etc. In the manufacturing process of recombinant human insulin used for the preparation of the MCB and WCB, various raw materials of biological origin are used. Moreover, in the preparation of the MCB and WCB for the manufacture of recombinant human insulin, bovine-derived peptones sourced from the US and Canada are used, and the Standards for Biological Ingredients are otherwise met.

Purity tests have been performed on the established MCB, WCB, and CAL, which have confirmed the absence of contaminating non-viral and viral infectious agents [see “Characterization and control of cell banks”]. As in-process controls, rodent parvovirus PCR at the pre-harvest stage has been set and moreover, mycoplasma testing, rodent parvovirus testing using 324K cells, and general virus screening on the harvested cell culture fluid have been set.

In order to confirm the ability of the purification process to remove/inactivate viruses, viral clearance was evaluated using xenotropic murine leukemia virus (X-MuLV) as a specific model virus, mouse minute virus (MMV) as a relevant virus, and simian virus 40 (SV40) as a non-specific model virus, and the results are as shown below.

Table. Viral clearance in the purification process

| Step | Viral clearance | | |
|-------------------------------------|-----------------|-----|-------|
| | X-MuLV | MMV | SV40 |
| █ treatment of █ pool (pH █) | ≥ █ | — | — |
| █ treatment of █ pool | ≥ █ | — | — |
| █ affinity chromatographic step | ≥ █ | █ | █ |
| █ ion exchange chromatographic step | ≥ █ | █ | ≥ █ |
| Total | ≥ 17.0 | 6.9 | ≥ 7.4 |

—: Not tested

2.A.(1).5 Manufacturing process development (Comparability)

The original site of Omalizumab manufacture was Genentech's [REDACTED] facility and in 20[REDACTED], the manufacture of the product was transferred to Genentech's [REDACTED] facility and then to Novartis Pharma's [REDACTED] facility.

The following changes have been made at Genentech's [REDACTED] facility.

- Although the drug product used in foreign phase I and II clinical studies was produced from the MCB and WCB prepared from a cell clone selected in medium containing [REDACTED] nmol/L methotrexate, the current drug product has been produced from the MCB and WCB prepared from a cell clone isolated in medium containing [REDACTED] μmol/L methotrexate.
- In the cell culture process, bovine peptone was switched to porcine peptone and the sterilization temperature was changed. Seed culture vessels were changed and medium change prior to initiating production culture was omitted. At the same time, the medium composition and the procedure for pH adjustment of production cultures were changed.
- In the purification process, to allow more efficient purification, a purification step by [REDACTED] ion exchange chromatography was added and then [REDACTED] ion exchange chromatography was switched to [REDACTED] ion exchange chromatography. Following the introduction of UF/DF ultrafiltration, the concentration process by size exclusion chromatography was abolished, but there have been no substantial changes in the order and method of purification.

When the manufacture of the product was transferred from Genentech's [REDACTED] facility to [REDACTED] facility, the procedure for pH adjustment of production cultures and the harvesting method were changed, and it has been determined that harvesting by [REDACTED] serves as an alternative to harvesting by [REDACTED] filtration. Omalizumab produced at [REDACTED] facility has a different carbohydrate profile from [REDACTED] product, but their clearance values are comparable and it has been confirmed that [REDACTED] product is comparable to [REDACTED] product.

Then, the manufacture of Omalizumab was transferred from Genentech's [REDACTED] facility to Novartis Pharma's [REDACTED] facility and the manufacturing process that is almost the same as that at [REDACTED] facility was employed [see "2.A.(1).3) Manufacturing process" for the changes made by Novartis Pharma] and production efficiency, physicochemical properties, biological properties, lot analysis, and stability were assessed. As a result, it has been confirmed that [REDACTED] product is comparable to [REDACTED] product.

2.A.(2) Drug substance

2.A.(2).1 Characterization

The drug substance has been characterized by N-terminal amino acid sequence, C-terminal amino acid sequence, free cysteine residues, peptide map, mass spectrometry, carbohydrate (monosaccharide

analysis, carbohydrate chain analysis, glycosylation), glycation, electrophoresis patterns, HPLC chromatographic behaviors, and biochemical properties.

- The N-terminal amino acid sequences of the heavy and light chains matched the amino acid sequences deduced from the DNA sequence.
- While [REDACTED] of C-terminal lysine 451 in the heavy chain has been cleaved by host cell basic carboxypeptidase, no C-terminal cleavage or heterogeneity was detected in the light chain.
- Intact Omalizumab has 32 cysteine residues with 4 intermolecular and 12 intramolecular disulfide bonds, but there was a variant in which the cysteine [REDACTED] and [REDACTED] residues of the heavy chain did not form disulfide bonds.
- After sulfitolysis of disulfide bonds, endoprotease Asp-N digested peptides were separated by reverse phase chromatography and analyzed by MALDI-TOF-MS and Edman sequencing. As a result, all the amino acid sequences of the heavy and light chains were determined. Glycosylation of the asparagine 301 residue of the heavy chain and oxidation of the methionine [REDACTED] and [REDACTED] residues of the heavy chain were found.
- The masses of Omalizumab and its heavy and light chains, as determined by mass spectrometry (ESI-MS) and reduced mass spectrometry, all matched the theoretical masses.
- The predominant glycoform of Omalizumab was of *N*-glycoside-linked complex biantennary structure consisting of fucose, *N*-acetylglucosamine, galactose, and mannose. In addition, 7 different glycoforms were identified. These glycoforms all have a basic structure containing 3 mannose molecules and 2 *N*-acetylglucosamine molecules. At least [REDACTED]% of Omalizumab was glycosylated.
- Glycation was found, but there were no differences in biological activity (it is inferred that no glycation has occurred at lysine residue in the CDR).
- The isoelectric point, as determined by capillary electrophoresis, was 7.6.
- SDS-PAGE under non-reducing conditions showed a main band at the molecular weight of approximately 180,000. Under reducing conditions, an approximately 28,000 band corresponding to the light chain and an approximately 55,000 band corresponding to the heavy chain were detected.
- Elution behaviors by hydrophobic interaction chromatography (after papain digestion), cation exchange chromatography, and size exclusion chromatography were elucidated.
- Omalizumab inhibited the binding of circulating IgE to the FcεRI receptor expressed on basophils and mast cells. Namely, it inhibited the ragweed-induced histamine release from these cells in a dose-dependent manner. When deglycosylated Omalizumab and intact Omalizumab were tested, there were no differences in the inhibitory activity according to the presence or absence of carbohydrate. When Omalizumab was forcibly degraded by heat, the inhibitory activity was decreased, but aggregation, light, and oxidation had no effects. Under acidic conditions, the activity was increased.

Potential product-related impurities include aggregates, Omalizumab fragments, the deglycosylated form, the glycated form, [REDACTED] adduct at the N-terminus of the heavy chain due to a different processing, a variant due to loss of C-terminal lysine 451 residue on the heavy chain, a variant in which cysteine [REDACTED] and [REDACTED] residues of the heavy chain do not form bonds, a variant due to isomerization of aspartic acid [REDACTED] residue of the light chain, and molecular variants due to oxidation or deamidation of constituent amino acids.

Process-related impurities include host cell-derived impurities (host cell proteins, host cell DNA) and gentamicin, insulin, Pluronic F-68, Tris base, and protein A, which are used in the manufacturing process. Process validation studies have confirmed that these are removed efficiently in the purification process. Therefore, host cell proteins are to be controlled by in-process control tests, but are not included in the specifications. Also, host cell DNA and [REDACTED] are not included in the specifications.

2.A.(2).2) Specifications

The proposed specifications for the drug substance include description, identification, pH, purity (for related substances, size exclusion chromatography, hydrophobic interaction chromatography, [REDACTED] ion exchange chromatography, SDS-capillary electrophoresis), osmolarity, bacterial endotoxins, polysorbate 20, strength (assay), and biological activity assay.

2.A.(2).3) Stability of the drug substance

The attributes tested in stability studies on the drug substance include description, pH, purity (for related substances, SDS-PAGE, CE-SDS-NGS, size exclusion chromatography, hydrophobic interaction chromatography, [REDACTED] ion exchange chromatography), biological activity, and strength (assay).

Long-term testing (-20°C, 49 or 60 months, 55 mL stainless steel tanks), accelerated testing (5°C, 1 month, 55 mL stainless steel tanks; 37°C, 32 days, 5 mL glass vials), and a study involving freeze/thaw cycles (three freeze/thaw cycles at -20°C and 5°C, 55 mL stainless steel tanks) were performed on the drug substance manufactured by Genentech. The drug substance was stable under the long-term and accelerated conditions (5°C, 1 month), but there were increases in related substances and a decrease in biological activity under the storage conditions of 37°C for 32 days. Up to three freeze/thaw cycles from -20°C to 5°C did not affect the quality of the drug substance.

Long-term testing (-20°C, 6 months, 55 mL stainless steel tanks) and accelerated testing (5°C, 6 months, 55 mL stainless steel tanks) were performed on the drug substance manufactured by Novartis Pharma and the drug substance was stable under these conditions. A comparative stability study of Novartis Pharma's product and Genentech's product (37°C, 32 days, 5 mL transparent glass vials) was performed, which showed that these products have comparable stability.

Based on the above, since Novartis Pharma's product has comparable stability to Genentech's product, the proposed shelf life for the drug substance is 60 months at -20°C and 1 month at 5°C when stored in stainless steel tanks. Freeze/thaw cycles from -20°C to 5°C may be repeated up to three times.

2.A.(3) Drug product

2.A.(3).1 Formulation development

Omalizumab is in the form of a lyophilized preparation in a 6 mL transparent glass vial stoppered with a butyl rubber stopper and each vial contains the components as listed below. An overage of 35% is used so as to deliver 150 mg of Omalizumab in 1.2 mL after reconstitution with 1.4 mL Water for Injection (the figures in the parentheses in the following table represent the actual amounts filled into each vial).

As an accompanying reconstitution diluent, Water for Injection (JP) will be attached.

| Component function | Name of component | Amount (mg) |
|--------------------|---------------------------------------|-------------|
| Active ingredient | Omalizumab (Genetical Recombination) | █ (202.5) |
| Buffer | L-histidine hydrochloride monohydrate | █ (2.8) |
| Buffer | L-histidine | █ (1.8) |
| Stabilizer | Sucrose | █ (145.5) |
| Stabilizer | Polysorbate 20 | █ (0.5) |

Initially, Omalizumab was developed as a █ formulation, but to meet the needs for █, █ lyophilisate was developed to allow █ adjustment. Although the full vacuum or partial vacuum products were used in clinical studies, the partial vacuum product was selected in the end.

As to the excipients used in the product, because L-histidine hydrochloride monohydrate has never been used for subcutaneous administration and L-histidine, sucrose, and polysorbate 20 exceed precedents when administered subcutaneously, they are all considered to be novel excipients. Concerning systemic toxicity and genotoxicity, since the amounts exceeding the maximum daily levels of the excipients used in the product have been administered intravenously, it has been determined that the safety of the excipients has already been confirmed. It has been determined that the results of the placebo group from repeated subcutaneous dose toxicity studies, a local tolerance study, etc. have confirmed the safety of the excipients up to the levels used in the drug product when it was administered subcutaneously.

2.A.(3).2 Drug product formulation process

The manufacturing process for the drug product is as shown below. The drug product to be marketed in Japan will be manufactured at Novartis Pharma's [REDACTED] facility.

| Manufacturing process | In-process control tests | Storage |
|---|---|--|
| <p>■ Thawing of bulk solution</p> <p>↓</p> | Identity testing, Protein content Bacterial endotoxins, pH | <p>Until the end of sterile filtration, [REDACTED] hours at [REDACTED]°C to [REDACTED]°C then, [REDACTED] hours [REDACTED]</p> |
| <p>■ Sterile filtration</p> <ul style="list-style-type: none"> · Filtration to remove microorganisms · Sterile filtration <p>↓</p> | For each, filter integrity test bioburden | |
| <p>■ Filling process</p> <ul style="list-style-type: none"> · Aseptic filling · Vials are partially stoppered with butyl rubber stoppers <p>↓</p> | Sterility test of filtrates [REDACTED] | [REDACTED] hours at [REDACTED]°C to [REDACTED]°C |
| <p>■ Lyophilization process</p> <ul style="list-style-type: none"> · Lyophilization · Vials are fully stoppered <p>↓</p> | | |
| <p>■ Capping process</p> <ul style="list-style-type: none"> · Vial capping · Rinsing of the outside of vials · Visual inspection of vials | | 2°C to 8°C |

Process validation was performed to evaluate the sterilization and depyrogenation (dry heat sterilization) of vials, steam sterilization of rubber stoppers, sterile filtration process, filter compatibility, lyophilization process, and aseptic process. As a result, it has been confirmed that the specified manufacturing process produces a drug product with good reproducibility.

2.A.(3).3 Specifications

The proposed specifications for the drug product include description, identification, pH, purity (for related substances, size exclusion chromatography, hydrophobic interaction chromatography, [REDACTED] ion exchange chromatography), reconstitution time, osmolarity, water content, bacterial endotoxins test, sterility test, foreign insoluble matter test for injections, insoluble particulate matter test for injections, uniformity of dosage unit, strength (assay), and biological activity assay.

2.A.(3).4 Stability of the drug product

The attributes tested in stability studies on the drug product include description, pH, identification (capillary electrophoresis), purity (for related substances, size exclusion chromatography, hydrophobic interaction chromatography, [REDACTED] ion exchange chromatography), water content, biological activity, insoluble particulate matter, and leakage.

Long-term testing (full vacuum, 5°C, up to 49 months; partial vacuum, 5°C, up to 36 months), accelerated testing (full vacuum, 30°C or 30°C/60%RH, 2 or 6 months; partial vacuum, 30°C, 6 months), and photostability testing (full vacuum, 725 W/m², 8 hours) were performed on the drug

product manufactured at a commercial scale by Genentech. Under the long-term and accelerated conditions, there were no changes from baseline in all attributes tested. In the photostability testing, no changes in the attributes tested were observed, indicating that there were no effects of light.

A comparative study of the partial vacuum product vs. the full vacuum product manufactured by Genentech (5°C or 30°C/60%RH, 6 months), a stability study to compare Genentech's product and Novartis Pharma's product (40°C/75%RH, 61 days), and long-term testing (partial vacuum, 5°C, 6 months) and accelerated testing (partial vacuum, 30°C/65%RH, 3 months) on the drug products manufactured by Novartis Pharma using the drug substance produced by Genentech and the drug substance produced by Novartis Pharma, were performed. As a result, there were no differences in the stability between the full and partial vacuum products and there were also no differences according to the manufacturing site. Under the long-term and accelerated conditions, the drug products were stable and there were no differences between the drug products manufactured using the drug substance produced by Genentech and the drug substance produced by Novartis Pharma. The long-term testing and accelerated testing are ongoing.

Based on the above, since Novartis Pharma's product has comparable stability to Genentech's product, the proposed shelf life for the drug product is 4 years at 5°C when stored in glass vials.

Although the drug product (manufactured by Genentech) was stable for up to 24 hours at 5°C and for up to 8 hours at 30°C following reconstitution, considering the maintenance of sterility in-use, the proposed package insert included the instruction that "the solution should be used within 8 hours when stored at 5°C or within 4 hours when stored at 30°C." In the course of the regulatory review, however, this instruction was changed to "the solution should be stored at 2°C to 8°C and used within 8 hours" [see "2.B Outline of the review by PMDA"].

2.A.(4) Reference material

The initial primary reference material has been characterized (N-terminal amino acid sequence, C-terminal amino acid sequence, free thiol residues, peptide map, mass spectroscopy, carbohydrate [monosaccharide analysis, carbohydrate chain analysis, glycosylation site, glycosylation rate], glycation, isoelectric point, electrophoresis patterns, HPLC chromatographic behaviors, biological properties) and assigned a specific activity of ■ × ■ units/mg.

The primary reference material² has also been tested for description, identification (trypsin-digested peptide map, receptor binding), related substances (size exclusion chromatography, hydrophobic interaction chromatography, ■ ion exchange chromatography, SDS-PAGE electrophoresis), fill weight, sucrose, polysorbate 20, biological activity, and strength (assay) in accordance with the specifications established during development. At the time of setting the current specifications, the

² The initial primary reference material is the current primary reference material.

primary reference material has been analyzed for identification (endoprotease Asp-N digested peptide map, capillary electrophoresis), purity (for related substances, size exclusion chromatography, hydrophobic interaction chromatography, SDS-capillary electrophoresis), osmolarity, polysorbate 20, and strength (assay).

The proposed specifications for working reference material include description, identification (endoprotease Asp-N digested peptide map), purity (for related substances, size exclusion chromatography, hydrophobic interaction chromatography, SDS-capillary electrophoresis), osmolarity, polysorbate 20, biological activity, and assay. With respect to the shelf life of the working reference material, the specification tests are to be performed every █ years and if the acceptance criteria are met, the shelf life is to be further extended for █ years from the original expiration date.

All reference materials are stored at █ ± █°C.

2.B Outline of the review by PMDA

2.B.(1) Conformity to the Standards for Biological Ingredients

Recombinant human insulin is used during the preparation of the MCB and WCB of Omalizumab. Because bovine peptones sourced from the US and Canada that do not meet the Standards for Biological Ingredients are used during the preparation of the MCB and WCB for the manufacture of recombinant human insulin, PMDA asked the applicant to explain risk assessment, the benefits of Omalizumab, and the timing of switching these raw materials.

The applicant explained as follows:

With respect to the risk of transmissible spongiform encephalopathy (TSE) infection associated with the use of these raw materials, “geographical risk for the countries of origin and risk of the specific parts used” and “risk taking account of treatment in the manufacturing process for the product and the usage” were assessed in accordance with the Attachment to the Notification No. 0801001 from the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 1, 2003. As a result, the total risk assessment score was “less than -3,” which met a threshold to provide a certain level of safety assurance. Thus, the risk of TSE infection associated with the use of Omalizumab should be very low. The medical benefit of Omalizumab is to offer a new treatment option for asthma management to severe patients whose symptoms are difficult to control with conventional asthma treatments. A new WCB will be generated using recombinant insulin that is produced without using raw materials of animal origin.

PMDA considers as follows:

Although the risk of TSE infection associated with Omalizumab cannot be excluded, the risk is very low and the medical benefits of Omalizumab for severe patients whose asthma symptoms are difficult to control with conventional asthma treatments outweigh the risks associated with the use of these raw materials. Thus, since this case falls under section 4-1-(5) of the Standards for Biological Ingredients,

there is no need to withhold the approval of Omalizumab until these raw materials are switched to those sourced from countries where no bovine spongiform encephalopathy (BSE) has been reported. However, it should be stated in the package insert that the risk of TSE infection cannot be excluded and it is necessary to fully explain it to patients prior to the use of Omalizumab. These conclusions are based on the premise that as soon as it becomes possible to manufacture a product conforming to the Japanese Standards, the current product will be replaced with the product that conforms to the Standards.

2.B.(2) Viral clearance

TaqMan assay (quantitative PCR) was used for the evaluation of viral clearance. PMDA asked the applicant to explain whether the evaluation by TaqMan assay can give the same results as the evaluation by infectivity assay.

The applicant responded as follows:

Concerning X-MuLV, Shi et al. have confirmed that for [REDACTED] ion exchange chromatographic step and the virus removal filtration step, the virus reduction factor determined by TaqMan assay is comparable to that determined by tissue-culture-infectious-dose assay (Shi L et al., *Biotechnology and Bioengineering*. 2004;87:884-896), but there are no data comparing TaqMan assay with tissue-culture-infectious-dose assay in [REDACTED] affinity chromatographic step. Because low-pH eluting solution (pH [REDACTED]) is used in [REDACTED] affinity chromatographic step for Omalizumab, X-MuLV in the eluate from the column is inactivated by low pH. Therefore, tissue-culture-infectious-dose assay evaluates both viral removal by column chromatography and inactivation of viruses by low pH as clearance capacity while TaqMan assay evaluates only the ability of column chromatography to remove viruses since X-MuLV RNA is stable even at low pH.

Concerning SV40, Shi et al. have confirmed that for [REDACTED] affinity chromatographic step, [REDACTED] ion exchange chromatographic step, and the virus removal filtration step, the virus reduction factor determined by TaqMan assay is comparable to that determined by tissue-culture-infectious-dose assay (Shi L et al., *Biologicals*. 1999;27:253-262).

Concerning MMV, Zhan et al. have confirmed that for [REDACTED] affinity chromatographic step and [REDACTED] ion exchange chromatographic step, the virus reduction factor determined by TaqMan assay is comparable to that determined by tissue-culture-infectious-dose assay (Zhan DJ et al., *Biologicals*. 2002;30:259-270).

Although TaqMan assay cannot assess virus infectivity, the literature has confirmed that for each virus, the virus reduction factor determined by TaqMan assay is comparable to that determined by tissue-culture-infectious-dose assay. Thus, PMDA accepted the response.

2.B.(3) C-terminal amino acids

Since the relative potency of a variant with heavy chain C-terminal Gly450/Lys451 (Gly450/Lys451 variant) was █%, PMDA asked the applicant to consider whether the specification for C-terminal amino acids should be provided.

The applicant explained as follows:

If the potency of Omalizumab reference material is 100%, the acceptable limits for biological activity correspond to █% to █% and the relative potency of the Gly450/Lys451 variant is █%, which is still within the acceptable limits for biological activity. Different lots contain █% to █% of the Gly450/Lys451 variant and the biological activities of these lots correspond to █% to █% and there were no differences among these lots. Furthermore, the Fab variant of Omalizumab binds to IgE, inhibiting the binding of IgE to the IgE receptor, and the C-terminus of the heavy chain is not involved in biological activity. Therefore, it is unnecessary to provide a specification for the content of the Gly450/Lys451 variant.

Although the relative potency of the Gly450/Lys451 variant is █% of reference material, the biological activities of the lots containing █% to █% of the Gly450/Lys451 variant were within the acceptable limits and there were no differences according to the content of the Gly450/Lys451 variant (Note: The biological activity of a lot containing █% of the Gly450/Lys451 variant has not been determined). Thus, PMDA accepted the applicant's response.

2.B.(4) Carbohydrate

Considering that there is no effect of carbohydrate on *in vitro* inhibitory activity, no specification for carbohydrate has been provided. However, PMDA asked the applicant to explain whether a specification for carbohydrate should be provided, taking account of its effects on consistent quality, pharmacokinetics, and *in vivo* efficacy and safety.

The applicant explained as follows:

(a) When lots with different carbohydrate profiles were intravenously administered to mice, there were no differences in clearance. (b) Although thrombocytopenia was observed in cynomolgus monkey and chimpanzee toxicity studies (high-dose administration), there has been no evidence that differences in carbohydrate content were associated with these changes. (c) In the manufacture of Omalizumab, there were little variations in the contents of glycoforms G0 and G1. Based on the above, since there are no effects on pharmacokinetics or safety and carbohydrate content during manufacture is consistent, it is unnecessary to provide a specification for carbohydrate.

PMDA accepted the above response because: (a) the study where Omalizumab with different carbohydrate profiles was administered to mice has only shown no changes in carbohydrate profile after administration, but generally in antibody preparations, differences in the carbohydrate profile are not considered to have a major impact on pharmacokinetics; (b) carbohydrate content did not affect the

safety of Omalizumab; (c) the primary mode of action of Omalizumab is the inhibition of IgE binding to its receptor and there were no differences in the inhibitory activity between intact and deglycosylated Omalizumab [see 2.A.(2).1) Characterization]; and (d) the submitted lots showed no major differences in the contents of glycoforms G0 and G1, as well as in glycoform composition, each glycoform content, and relative abundance of glycoform G1.

2.B.(5) Specification limits

PMDA asked the applicant to explain (a) the reason for differences in the specification limits for purity of the drug product between foreign countries and Japan, (b) the reason why “molecular weight size” and “degradation products/related substances” of the drug product testing after lyophilization are different from the specification limits for the drug product, and (c) the reason why the specification limits for purity of the drug product are different from those of the drug substance, despite the fact that the main manufacturing process steps for the drug product are sterile filtration, filling, and lyophilization only.

The applicant responded as follows:

In foreign countries, release and end-of-shelf-life specifications have been established to perform quality control.

- (a) The presented specification limits are the overseas release limits. Because the Japanese specification limits are the shelf-life limits, the numerical values are different, but the overseas shelf-life limits are the same as the Japanese specification limits.
- (b) The acceptable limits after lyophilization are based on the overseas release specification, which are tighter than the overseas shelf-life limits and the Japanese specification limits.
- (c) Tighter specification limits have been established for the drug substance than for the drug product in order to assure conformance to the end of shelf-life specification for the drug product. Although the release limits for the product are the same as the shelf-life limits for the drug substance, shelf-life limits that are different from the release limits have been established based on the results of stability studies.

PMDA accepted the above responses since the presented overseas specification limits are the release limits and the Japanese specification limits, which are shelf-life limits, are the same as the overseas shelf-life limits.

2.B.(6) Stability after reconstitution

The information on the stability after reconstitution is available in the Basic Prescribing Information, overseas package inserts, etc. PMDA asked the applicant to provide a justification for the shelf life after reconstitution specified in these documents and consider whether this information should be provided also in the Japanese package insert.

The applicant responded as follows:

When 3 lots of the drug product (at release, after 36 months storage at 5°C) were reconstituted and then stored at 5°C for 48 hours or at 30°C for 24 hours, there were no marked differences from baseline and the solution was stable. However, to provide more stringent rules, the labeling includes the instruction that “the solution should be used within 8 hours following reconstitution when stored at 2°C to 8°C.” It has been decided to adopt this instruction also in Japan and include it in the Precautions concerning Use section of the package insert. In addition, since the preparation procedure for Omalizumab administration is complicated, a separate leaflet to be attached with the package insert to the product will be developed in order to provide information on the preparation procedure.

PMDA accepted the above responses.

2.B.(7) Novel excipients

The drug product contains the following novel excipients: sucrose as a stabilizer, L-histidine hydrochloride monohydrate and L-histidine as buffers, and polysorbate 20 as a stabilizer.

These excipients all conform to the compendial specifications (sucrose, Japanese Pharmacopoeia; L-histidine hydrochloride monohydrate and L-histidine, Japanese Pharmaceutical Codex; polysorbate 20, Japanese Pharmaceutical Excipients) and PMDA concluded that there are no problems with the specifications and the stability.

Regarding safety, because all of these excipients have been administered intravenously at exposure levels exceeding the amounts used in the proposed dose regimen, PMDA concluded that there are no problems in terms of systemic toxicity and genotoxicity. As to toxicity at injection site (local tolerance), it was inferred, based on the submitted data, that even if these excipients are subcutaneously administered at levels that are contained in the product, clinically relevant findings are unlikely to occur.

Based on the above, PMDA concluded that there are no particular problems with the use of these excipients in the product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

In this application, anaphylactogenicity, immune complexes with IgE, IgE binding affinity and the mode of inhibition, and anti-IgE effects have been investigated as primary pharmacodynamic studies. No secondary pharmacodynamic, safety pharmacology, or pharmacodynamic drug interaction studies have been conducted. However, the safety pharmacology core battery has been conducted as part of repeat-dose toxicity studies in cynomolgus monkeys (4.2.3.2-2, 4.2.3.2-3, 4.2.3.2-4, 4.2.3.7.3-4).

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

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

3.(i).A.(1.1) Anaphylactogenicity studies

(a) Epitope mapping (4.2.1.1-2 and 4.2.1.1-3)

Human IgE variants with amino acid residue substitutions were generated and the amino acid residues within the human IgE epitope required for binding were identified by investigating their binding to human high-affinity IgE receptor (FcεRI), Omalizumab (Genetical Recombination), and its parental murine anti-human IgE antibody before humanization (MaE11). As a result, the recognition site for human FcεRI was 6 amino acid residues (380, 408, 411, 452, 465, 469) and the recognition site for Omalizumab and MaE11 was [REDACTED] amino acid residues including 5 amino acids for human FcεRI ([REDACTED] and [REDACTED]).

Based on the above results, the applicant explained that because Omalizumab cannot bind to IgE bound to FcεRI which results in inability to cross-link IgE, Omalizumab is non-anaphylactogenic.

(b) Ability to bind IgE bound to human basophils (4.2.1.1-4)

Human IgE bound to human basophils was added with biotinylated Omalizumab or goat anti-human IgE antibody capable of inducing allergic reactions and fluorescence-activated cells were analyzed by flow cytometry, which indicated that goat anti-human IgE antibody binds IgE bound to FcεRI but Omalizumab does not.

(c) Histamine release from human basophils (4.2.1.1-4)

Peripheral blood basophils prepared from 12 donors were sensitized with human serum containing ragweed-specific IgE to investigate histamine release when added with ragweed antigen, Omalizumab, or a murine anti-human IgE antibody capable of inducing allergic reactions (MaE1). As a result, while there were clear increases in the amount of histamine release following the addition of ragweed antigen and MaE1, the amount of histamine release following the addition of Omalizumab was similar to that of vehicle.

3.(i).A.(1.2) Investigation of immune complexes with IgE

(a) Molecular weight and molar ratio (4.2.2.3-1)

Following the intravenous administration of ¹²⁵I-labeled Omalizumab to the cynomolgus monkey, the molecular weight of immune complexes formed between Omalizumab and IgE in the collected serum was determined by chromatography. As a result, the molecular weight of immune complexes varied as the molar ratio of Omalizumab to endogenous IgE was changed, but complexes larger than 1 million in molecular weight were not observed.

Based on the above results, the applicant discussed that the largest complex formed between Omalizumab and IgE is a heterohexamer consisting of 3 Omalizumab molecules and 3 IgE molecules and the types of complexes formed and their relative ratios depend on the molar ratio of Omalizumab

to IgE.

(b) Complement-dependent cytotoxicity (4.2.1.1-6)

Human embryonic kidney 293 cells expressing human IgE on their surface were pretreated with ^{51}Cr and added with Omalizumab (IgG1 antibody), a variant form of Omalizumab of IgG3 subclass exhibiting a strong complement-activation capacity, or a murine anti-human IgE antibody (IgG2b antibody), and then complement components were added to the cells to investigate complement-dependent cytotoxicity by determining supernatant radioactivity. As a result, the positive control, i.e. a murine anti-human IgE antibody (IgG2b antibody) and the IgG3 variant of Omalizumab at 0.01, 0.1, and 1.0 $\mu\text{g}/\text{mL}$ increased the cytolysis rate in a concentration-dependent manner, but the addition of Omalizumab did not induce cytolysis. While complexes formed between the IgG3 variant of Omalizumab and IgE showed high C1q binding capacity, the C1q binding capacity of Omalizumab (IgG1 antibody)-IgE complexes was similar to that of IgE alone.

3.(i).A.(1).3 Investigation of IgE binding affinity and mode of inhibition

(a) Human IgE binding affinity (4.2.1.1-7, 4.2.1.1-9)

The binding affinity of Omalizumab to human IgE was investigated under various experimental conditions. The K_d value of Omalizumab for IgE expressed on the surface of human embryonic kidney 293 cells was about 0.2 nM. The K_d values of Omalizumab and the Fab fragment of Omalizumab for IgE determined using a surface plasmon resonance sensor were 7.7 nM and 15.5 nM, respectively.

(b) Mode of inhibition (4.2.1.1-10)

Using CHO-3D10 cells expressing a molecule consisting of the α -subunit extracellular domain of human Fc ϵ RI and the transmembrane and intracellular domains of the human IL-2 receptor, the mode of inhibition of human IgE binding to human Fc ϵ RI by Omalizumab was investigated. The binding of human ^{125}I -IgE to Fc ϵ RI on the surface of CHO-3D10 cells was measured in the presence of various concentrations of Omalizumab. As a result, Omalizumab did not affect maximum binding of human ^{125}I -IgE to Fc ϵ RI (B_{max}) and caused a rightward shift in the binding response curve and Lineweaver-Burke plot analysis showed that the mode of inhibition was competitive. Based on Omalizumab concentrations and apparent K_d value, the K_i value of Omalizumab was calculated to be 1.0 nM.

3.(i).A.(1).4 Investigation of anti-IgE effects

(a) Inhibition of IgE rebinding (4.2.1.1-11)

Human ^{125}I -IgE was bound to CHO-3D10 cells and the effects of Omalizumab on a decrease in the amount bound over time were investigated. The addition of Omalizumab promoted a decrease in ^{125}I -IgE bound to the cells and the dissociation rate (k_{off} value) was 293 hour^{-1} , which was about 1.5 fold the value without Omalizumab (199 hour^{-1}).

Based on the above results, the applicant discussed that Omalizumab trapped free IgE and inhibited

the rebinding of IgE to FcεRI.

(b) Reduction of free IgE levels (4.2.1.1-12)

The effects of 0.1 to 100 µg/mL of Omalizumab on free IgE levels in serum of [REDACTED] patients were investigated. Individual serum IgE levels were 493, 1596, and 3792 ng/mL. The addition of Omalizumab reduced free IgE levels concentration-dependently and even the serum IgE level of 3792 ng/mL was reduced to ≤ 25 ng/mL, which was the clinical target level [see “4.(ii) Summary of clinical pharmacology studies”], following the addition of 80 µg/mL of Omalizumab. Omalizumab concentrations required to reduce free IgE levels to ≤ 25 ng/mL were 16- to 21-fold the IgE levels.

(c) Inhibition of histamine release from rat basophils (4.2.1.1-13)

Rat basophils expressing human FcεRI α-subunit (RBL-48 cells) were sensitized with ragweed-specific human IgE to investigate the effects of Omalizumab on histamine release induced by the addition of ragweed antigen. When 0.078 to 10 nM of Omalizumab was added at the same time as sensitization with ragweed-specific human IgE, Omalizumab concentration-dependently inhibited histamine release and its IC₅₀ value was 1.88 nM.

(d) Inhibition of IgE production (4.2.1.1-15)

Using peripheral blood monocytes obtained from patients with cat allergy, the effects of Omalizumab on IgE production induced by the addition of IL-2, IL-4, and cat dander were investigated. The addition of IL-2 and IL-4 to human monocytes sensitized with cat antigen increased the IgE level in the culture supernatant and the further addition of the antigen, cat dander, doubled the IgE level. Meanwhile, when IL-2, IL-4, and cat dander were added in the presence of 0.002 to 1 µg/mL of Omalizumab, IgE production was inhibited in a concentration-dependent manner and it was reduced to about one-third at ≥ 0.25 µg/mL. Since Omalizumab does not bind to IgE bound to FcεRI but may bind to IgE expressed on the cellular membrane (mIgE), immunofluorescent staining of CD19⁺ B cells in peripheral blood monocytes with Omalizumab was performed. As a result, approximately 6% of the cells were stained.

Based on the above results, the applicant discussed the possibility that Omalizumab may bind to mIgE on B cells, inhibiting the activation and proliferation of B cells, which reduces IgE production. On the other hand, the applicant explained that Omalizumab had no effect on IgE production in a clinical study in patients with allergic rhinitis (5.3.1.1-3).

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

PMDA asked the applicant to explain the reason for not conducting a study in an *in vivo* bronchial asthma model using cynomolgus monkeys etc.

The applicant explained as follows:

At the time of initiating a pharmacological investigation (around 19[REDACTED]), a relevant allergic asthma

model using cynomolgus monkeys etc. responsive to Omalizumab for performing pharmacological evaluation had not been established. Therefore, the necessity of evaluating the effects of Omalizumab against allergic asthma was considered, but it was impossible to do so. In recently established rhesus monkey asthma model (Schelegle ES et al., *Am J Pathol.* 2001;158:333-341) and cynomolgus monkey asthma model (Van Scott MR et al., *J Appl Physiol.* 2004;96:1433-1444), exposure to aerosolized house dust causes an increase in antigen-specific IgE and these animal models are likely to be capable of evaluating the effects of Omalizumab against allergic asthma appropriately. However, because foreign clinical studies had already been completed or the product had already been introduced into the market at the time of publication of these models, evaluation using an animal model was not performed.

Since the submitted data including the above study results have shown that Omalizumab neutralizes free IgE without binding to IgE bound to FcεRI, PMDA concluded that it can be justified that an adequate clinical dose of Omalizumab can inhibit allergic reactions mediated by free IgE.

3.(ii) Summary of pharmacokinetic studies

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

The results of pharmacokinetic studies of intravenous or subcutaneous Omalizumab (Genetical Recombination) in mice and monkeys were submitted.

Omalizumab concentrations in sample diluent and mouse serum were quantitated by an enzyme immunoassay (ELISA) detecting recombinant humanized IgG (lower limit of quantification, ■■■ ng/mL) and free Omalizumab concentrations in monkey serum and matrix etc. were quantitated by an ELISA specific to Omalizumab using IgE derived from human myeloma cell line U266 as a capture antigen (lower limit of quantification, ■■■ ng/mL). Murine anti-Omalizumab antibodies and monkey anti-Omalizumab Fab and Fc antibodies were quantitated using an ELISA with Omalizumab or Omalizumab-derived Fab and Fc fragments immobilized on the plate (lower limit of quantification, antibody titer = ■■■). Total IgE (the sum of free IgE and IgE in Omalizumab-IgE complexes) concentrations in monkey serum were quantitated by an ELISA using FcεRI-IgG chimeric receptor with the IgE binding site similar to Omalizumab as a capture reagent (lower limit of quantification, ■■■ ng/mL). Free IgE concentrations were quantitated by an ELISA using murine anti-human IgE antibody as a capture antigen (lower limit of quantification, ■■■ ng/mL) or by flow cytometric analysis using CHO cell line expressing the α-subunit of the human FcεRI receptor (quantification limit, ■■■ μg/mL). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

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

(a) Single-dose studies

Following a single intravenous dose of 5 mg/kg of Omalizumab to female mice (n = 10), the terminal phase half-life ($t_{1/2}$) was about 2.1 weeks, clearance (CL) was 4.13 mL/day/kg, and steady-state

distribution volume (V_{ss}) was 93.5 mL/kg. Murine anti-human antibody (MAHA) was not detected (4.2.2.2-1).

Following single intravenous doses of 1, 10, and 100 mg/kg of Omalizumab to male mice (n = 32 per group), the t_{1/2} was 22 to 23 days and the V_{ss} was 91.9 to 95.9 mL/kg. Following a single subcutaneous dose of 10 mg/kg of Omalizumab to CD-1 male mice (n = 32 per group), clearance (CL/F) was 3.31 mL/day/kg, the area under the serum drug concentration-time curve (AUC) was 3020 day·µg/mL, and the absolute bioavailability (BA) was 92.2%. MAHA was detected in a total of 3 mice, which did not affect the pharmacokinetics of Omalizumab (4.2.2.2-2).

The pharmacokinetic parameters following single subcutaneous doses of 0.5, 5, and 25 mg/kg of Omalizumab or single intravenous doses of 0.5 and 5 mg/kg of Omalizumab in male cynomolgus monkeys (n = 3 per group) are as shown in the following table. After a single subcutaneous dose of 25 mg/kg, the ratio of AUC between the doses exceeded the ratio of the doses and the t_{1/2} was prolonged (4.2.2.2-4). There was a trend that with increasing dose, serum total IgE levels after the administration of Omalizumab increased while free IgE levels declined correspondingly (4.2.2.3-2) (4.2.2.3-3) (4.2.2.3-4). No anti-Omalizumab antibody was detected.

Table. Pharmacokinetic parameters following subcutaneous or intravenous administration of Omalizumab in monkeys

| Pharmacokinetic parameter | Subcutaneous administration | | | Intravenous administration | |
|---------------------------|-----------------------------|-------------|--------------|----------------------------|-------------|
| | 0.5 | 5 | 25 | 0.5 | 5 |
| Dose (mg/kg) | 0.5 | 5 | 25 | 0.5 | 5 |
| C _{max} (µg/mL) | 4.70 ± 0.458 | 55.5 ± 8.05 | 254 ± 29.1 | 20.7 ± 10.4 | 158 ± 5.33 |
| T _{max} (day) | 5.33 ± 4.51 | 5.17 ± 3.18 | 2.83 ± 1.89 | NA | NA |
| CL/F (mL/day/kg) | 5.16 ± 1.55 | 4.55 ± 1.30 | 3.07 ± 0.721 | 4.46 ± 1.04 | 4.66 ± 1.09 |
| V _{ss} (mL/kg) | NA | NA | NA | 58.8 ± 3.98 | 53.2 ± 7.28 |
| AUC (day·µg/mL) | 102 ± 26.7 | 1160 ± 315 | 8460 ± 1990 | 116 ± 27.3 | 1110 ± 229 |
| F (%) | 88 | 104 | NA | NA | NA |
| t _{1/2} (day) | 11.5 ± 2.95 | 10.3 ± 1.84 | 17.7 ± 7.35 | 9.94 ± 2.86 | 8.53 ± 2.57 |

Mean ± SD (n = 3), C_{max}: Maximum serum concentration, T_{max}: Time to maximum concentration, F: Absolute BA, NA = Not analyzed

¹²⁵I-human IgE was administered to male and female cynomolgus monkeys after intravenous administration of 5 mg/kg of Omalizumab. The CL of ¹²⁵I-IgE in the absence of Omalizumab was 52.8 ± 12.0 mL/day/kg (n = 6) while the CL of ¹²⁵I-IgE in the presence of Omalizumab was 20.6 ± 3.62 mL/day/kg (n = 3), showing a reduction in the clearance of IgE due to complex formation with Omalizumab (4.2.2.3-2). Omalizumab-IgE complexes (heterotrimer [Omalizumab:IgE = 2:1] and heterohexamer [Omalizumab:IgE = 3:3]) and Omalizumab-murine anti-IgE monoclonal antibody-IgE complexes (molecular weight ≥ 4 million), following the addition of ¹²⁵I-IgE, were intravenously administered to male monkeys (n = 3 per group). As a result, the clearance of Omalizumab-IgE complex was correlated with the number of Fcγ domains of the complex and the order of clearance of these complexes was Omalizumab-murine anti-IgE monoclonal antibody-IgE complex (molecular weight ≥ 4 million) > heterohexamer > heterotrimer > Omalizumab (4.2.2.3-3) (4.2.2.3-4).

Omalizumab (¹²⁵I- or Cy3-labeled) alone or Omalizumab-IgE complexes were intravenously administered to recombination activation gene-2 (RAG-2) deficient (KO) mice lacking

immunoglobulin G (IgG) to investigate the clearance of the complexes. The uptake into the liver and spleen at 30 minutes post-dose increased depending on the molecular weight of the complexes and was higher in RAG-2 KO mice than in wild-type mice, which suggested that endogenous IgG competes with Omalizumab-IgE complex for binding to the Fc γ receptor. Electron microscopy showed localization of Omalizumab-IgE complexes in hepatic sinusoidal endothelial cells and Kupffer cells as well as spleen macrophages. Marked decreases of Omalizumab-IgE complexes in all organs tested were seen at 10 hours post-dose. No Omalizumab-IgE complexes were detected in the kidney at any timepoint (4.2.2.3-5).

(b) Repeat-dose studies (TK studies)

Omalizumab (0, 0.1, 1, 5 mg/kg) was administered intravenously or subcutaneously 3 times weekly for 4 weeks to male and female cynomolgus monkeys (n = 2-10 per group). With increasing dose, the AUC₀₋₂₈ and C_{max} increased, and total IgE levels were elevated while free IgE levels declined. The BA in the 5 mg/kg subcutaneous administration group was 70.2% to 92.4% (4.2.3.2-2).

Omalizumab (0.1, 1, 5 mg/kg) was administered intravenously or subcutaneously 3 times weekly for 6 months to male and female cynomolgus monkeys (n = 2-10 per group). After intravenous and subcutaneous administration of 5 mg/kg, the AUC₀₋₂₈ tended to increase more than proportionally to the dose. In the dose groups where serum Omalizumab levels exceeded total IgE levels (intravenous administration of 5 mg/kg, subcutaneous administration of 1 and 5 mg/kg), total IgE levels increased and reached a steady-state after 3 to 4 weeks of treatment with Omalizumab (4.2.3.2-3).

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

Following a single intravenous dose of ¹²⁵I-labeled Omalizumab 0.03 mg/kg alone or in combination with unlabeled Omalizumab 0.51 mg/kg to male and female cynomolgus monkeys (n = 3), the volume of distribution was almost the same as the plasma volume. When tissue Omalizumab concentrations at 1 hour and 96 hours post-dose were determined, no specific uptake by any tissue was clearly noted and there was no distribution into blood cells (4.2.2.3-1).

Pregnant cynomolgus monkeys (n = 12 per group) were subcutaneously administered Omalizumab (0, 3, 15, 75 mg/kg) on gestation days 20, 21, 22, 29, 36, 43, and 50. In maternal animals, the C_{max} of Omalizumab at 3, 15, and 75 mg/kg was 119, 507, and 2540 μ g/mL, respectively, the AUC₂₀₋₉₉ was 3630, 18500, and 95200 day \cdot μ g/mL, respectively, and the t_{1/2} was 6.71 to 9.93 days. Omalizumab concentrations in cord serum increased in proportion to the dose and were about 28% to 36% of maternal serum levels, and Omalizumab concentrations in amniotic fluid were about 4% to 8% of cord serum levels (4.2.3.5.2-1). Furthermore, pregnant cynomolgus monkeys (n = 8 per group) were subcutaneously administered Omalizumab (0 and 75 mg/kg) once daily on gestation days 120 to 122 and once weekly through gestation days 127 to 148 or lactation day 28. As a result, Omalizumab was detected in amniotic fluid (3.3% of maternal serum level on gestation day 148), milk (0.154%), fetal serum (32.9%), and neonatal serum (33.2%) (4.2.3.5.3-1). A caution statement about placental transfer

and excretion into milk is included in the “4. Use during pregnancy, delivery or lactation” section of the package insert.

3.(ii).A.(3) Metabolism

Following a single intravenous dose of ¹²⁵I-labeled Omalizumab 0.03 mg/kg alone or in combination with unlabeled Omalizumab 0.51 mg/kg to cynomolgus monkeys, no metabolites of Omalizumab were detected in the systemic circulation.

3.(ii).A.(4) Excretion

Following a single intravenous dose of Omalizumab (¹²⁵I-labeled Omalizumab) 0.03 mg/kg alone or in combination with unlabeled Omalizumab 0.51 mg/kg to cynomolgus monkeys, 41% to 65% of the administered radioactivity was excreted in urine up to 96 hours post-dose and ≤ 0.5% of the administered radioactivity was excreted in feces (4.2.2.3-1). The majority of radioactivity excreted in urine was not precipitated by the addition of trichloroacetic acid and the unchanged drug or IgE was not detected by Western blotting (4.2.2.3-1).

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

PMDA asked the applicant to explain the mechanism of elevation of total IgE levels after the administration of Omalizumab.

The applicant explained as follows:

In the study where ¹²⁵I-human IgE was administered to male and female cynomolgus monkeys after intravenous administration of Omalizumab, the clearance of ¹²⁵I-IgE was lower in the presence of Omalizumab than in the absence of Omalizumab. Elevations of total IgE levels were observed also in clinical studies. Thus, the cause of such elevation was investigated based on the results of population pharmacokinetic-pharmacodynamic analysis (5.3.3.5-4). As a result, it was indicated that the order of clearance is free IgE ($CL_{E/f}$, 71.0 mL/h) > Omalizumab-IgE complexes ($CL_{C/f}$, 13.2 mL/h) > free Omalizumab ($CL_{X/f}$, 7.32 mL/h), which suggested that elevation of total IgE levels after the administration of Omalizumab may be attributable to a reduction in the clearance of IgE due to the formation of Omalizumab-IgE complexes. Namely, it is inferred that total IgE levels are elevated because the clearance of Omalizumab-IgE complexes is lower compared to that of free IgE which binds to high-affinity FcεR1 expressed on the surface of mast cells, basophils, etc. and is eliminated by non-specific proteolysis while Omalizumab-IgE complexes are eliminated by the degradation process via low-affinity FcγR expressed on monocytes, macrophages, neutrophils, etc.

PMDA accepted the applicant’s response.

PMDA asked the applicant to provide a justification for omitting a detailed investigation of metabolism and excretion of Omalizumab.

The applicant explained as follows:

When a humanized antibody drug is administered to animals, neutralizing antibody will be produced, which makes evaluation difficult. As with other marketed antibody drugs, therefore, non-clinical pharmacokinetics of Omalizumab have been studied in monkeys that are relatively close to humans. A particular investigation of metabolism has not been conducted because an antibody drug, similarly to endogenous human IgG, is considered to be metabolized via the reticuloendothelial system (primarily, proteolysis by endopeptidase) and excreted as low molecular weight peptides and amino acids, and Omalizumab is also likely to follow a similar metabolic pathway. Regarding excretion, using ¹²⁵I-labeled Omalizumab, the excretion rates of the administered radioactivity and excretion of the unchanged drug were determined.

Based on the evaluation of the submitted pharmacokinetic data, PMDA concluded that Omalizumab has similar pharmacokinetic properties to human IgG and accepted the applicant's response.

Because Omalizumab concentrations were higher in the liver than in other organs in the tissue distribution study in cynomolgus monkeys, PMDA asked the applicant to explain whether the accumulation of Omalizumab in the liver raises a safety concern.

The applicant explained as follows:

(a) When tissue radioactivity levels at 96 hours post-dose in the tissue distribution study were compared, radioactivity levels were higher in the liver, kidney, and lung where blood vessels are concentrated than in other organs, but these levels were lower than blood levels and were not extremely high compared to those in other organs and tissues. (b) No histological changes in the liver were observed in repeat-dose toxicity studies. (c) There were no major differences in the incidence of adverse events of abnormal liver function tests and hepatic dysfunction between the Omalizumab and placebo groups in Japanese and foreign clinical studies, and also according to overseas post-marketing safety information, there are not many spontaneous reports of adverse events of hepatic dysfunction. Therefore, the risk of liver disorder associated with Omalizumab is small and there should be little effects of continued treatment.

PMDA considers as follows:

Extreme accumulation of Omalizumab or histological changes in the liver have not been observed and there have been no major problems in a clinical setting so far, but it is necessary to further investigate the safety in patients with hepatic impairment etc. through post-marketing surveillance.

3.(iii) Summary of toxicology studies

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

The results from the following toxicity studies of Omalizumab (Genetical Recombination) were submitted: single-dose toxicity studies, repeat-dose toxicity studies, a genotoxicity study, reproductive and developmental toxicity studies, local tolerance studies, and studies to investigate the mechanism

of effects on platelets. No carcinogenicity or antigenicity study has been performed since there is no relevant test system.

3.(iii).A.(1) Single-dose toxicity

Single-dose toxicity studies were conducted by the intravenous route in mice (4.2.3.1-1), the intravenous route in cynomolgus monkeys (4.2.3.1-3, 4.2.3.1-4), and the subcutaneous route in cynomolgus monkeys (4.2.3.1-2, 4.2.3.1-4). In a mouse intravenous toxicity study, anti-Omalizumab antibodies were detected in some mice, but there were no changes in clinical observations etc. and the approximate lethal dose was determined to be ≥ 100 mg/kg. In cynomolgus monkey intravenous and subcutaneous toxicity studies, there are increases in serum total IgE levels and decreases in free IgE levels, and anti-Omalizumab Fab antibodies were noted, but there were no changes in clinical observations etc. The approximate lethal doses by intravenous and subcutaneous administration were determined to be ≥ 200 mg/kg and ≥ 50 mg/kg, respectively.

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

Repeat-dose toxicity studies conducted include a mouse 4-week intravenous toxicity study (4.2.3.2-1), a cynomolgus monkey 4-week subcutaneous and intravenous toxicity study (4.2.3.2-2), a cynomolgus monkey 6-month subcutaneous and intravenous toxicity study (4.2.3.2-3), and a juvenile cynomolgus monkey 26-week subcutaneous toxicity study (4.2.3.2-4).

In the mouse 4-week intravenous study, Omalizumab (0, 1, 10, 50 mg/kg) was administered once weekly and a 4-week recovery period was scheduled for a proportion of control and 50 mg/kg animals. No changes in clinical observations were noted and there were no abnormalities in body weight, food consumption, ophthalmic examination, laboratory tests, necropsy, and histopathologic examination. The no observed adverse effect level (NOAEL) was determined to be 50 mg/kg. No anti-Omalizumab antibody was detected throughout the dosing and recovery periods.

In the cynomolgus monkey 4-week subcutaneous and intravenous study, Omalizumab (0, 0.1, 1, 5 mg/kg) was subcutaneously or intravenously administered 3 times weekly. No changes in clinical observations were noted and there were no abnormalities in body weight, food consumption, physical examination, blood pressure and ECG, ophthalmic examination, laboratory tests, and necropsy and histopathologic examination. The NOAELs for subcutaneous and intravenous administration were both determined to be 5 mg/kg. The 1- and 5-mg/kg groups exhibited increases in total IgE levels and decreases in free IgE levels. Anti-Omalizumab Fab antibodies were detected in a total of 3 animals (1 of 8 animals in the subcutaneous 1-mg/kg group,³ 1 of 10 animals in the subcutaneous 5-mg/kg group,³ 1 of 2 animals in the intravenous 0.1-mg/kg group³).

In the cynomolgus monkey 6-month subcutaneous and intravenous study, Omalizumab (0, 0.1, 1, 5

³ The denominator for the number of animals with antibodies is the number of animals in each group, not the number of animals tested.

mg/kg) was administered 3 times weekly for 6 months, or for the purpose of evaluating intermittent administration, 5 mg/kg was administered 3 times weekly on Study Days 1 to 59 and 122 to 183. No changes in clinical observations were noted and there were no abnormalities in body weight, food consumption, physical examination, blood pressure and ECG, ophthalmic examination, and laboratory tests. Necropsy revealed an increased incidence of red lesions at the injection site in females in the subcutaneous 5-mg/kg group and histopathologic examination showed increased incidences of hemorrhage and infiltrations of subcutaneous lymphohistiocytes and eosinophils at the injection site in the subcutaneous administration groups. These histological changes are considered to be local immune reactions to repeated administration of a heteroprotein and the NOAELs for subcutaneous and intravenous administration were both determined to be 5 mg/kg. In order to assess the ability of Omalizumab to induce allergic reactions, intradermal test was performed at Study Week 27. As a result, moderate swelling was noted in all animals in the intermittent subcutaneous and intravenous administration groups (10 animals), but 6 out of these 10 animals exhibited a similar reaction also at the injection site of saline. Increases in total IgE levels and decreases in free IgE levels were observed in almost all animals treated with Omalizumab, and anti-Omalizumab Fab antibodies were detected in 1 of 8 animals in the subcutaneous 0.1-mg/kg group,⁴ 2 of 8 animals in the subcutaneous 1-mg/kg group,⁴ 2 of 10 animals in the subcutaneous 5-mg/kg group,⁴ and 4 of 8 animals in the intermittent subcutaneous 5-mg/kg group.⁴

In the juvenile cynomolgus monkey 26-week subcutaneous study, Omalizumab (0, 50, 250 mg/kg) was administered once weekly and a 26-week recovery period was scheduled for a proportion of control and 250 mg/kg animals. Thrombocytopenia was observed in all Omalizumab groups. Prolonged bleeding time was noted in the 250-mg/kg group and mild to moderate increases in bone marrow megakaryocytes were seen in the 50- and 250-mg/kg groups and histopathologic examination revealed hemorrhage in the subcutaneous tissue at the injection site, in seminal vesicles, in the stomach fundus mucosa, or in the duodenal mucosa of limited animals in the 50- and 250-mg/kg groups. These were considered to be changes related to decreases in peripheral blood platelet counts, which all resolved after a 26-week recovery period. In order to investigate the effects on the immune system, serum IgG, IgA, and IgM levels were measured. As a result, there were increases in IgM and IgG levels, which were both within the normal ranges. In addition, increases in total IgE levels and decreases in free IgE levels were observed and anti-Omalizumab Fab antibodies were detected in 3 of 12 animals in the 250-mg/kg group.⁴ No other changes in clinical observations etc. were noted and the NOAEL was determined to be < 50 mg/kg.

3.(iii).A.(3) Genotoxicity

Omalizumab was not mutagenic in a bacterial reverse mutation assay (4.2.3.3.1-1).

⁴ The denominator for the number of animals with antibodies is the number of animals in each group, not the number of animals tested.

3.(iii).A.(4) Reproductive and developmental toxicity

Reproductive and developmental toxicity studies were conducted only in cynomolgus monkeys because Omalizumab does not bind to murine or rat IgE and there are no surrogate proteins that are non-antigenic for mice or rats.

In a male fertility study in cynomolgus monkeys by subcutaneous administration, Omalizumab (0, 3, 15, 75 mg/kg) was administered once daily on Days 1 to 3 and then once weekly for 6 weeks. All animals exhibited normal mating behavior and there were increases in serum total IgE levels in all Omalizumab groups. No other abnormalities including those in clinical observations were noted and the NOAEL was determined to be 75 mg/kg (4.2.3.5.1-1).

In a cynomolgus monkey study for effects on female fertility and early embryonic development to implantation by subcutaneous administration, Omalizumab (0, 3, 15, 75 mg/kg) was administered once daily on the 2nd to 4th day of the 3rd menstrual cycle after the end of observation period (2 menstrual cycles) and then once weekly for a total of 3 menstrual cycles (or 13 weeks) before mating, during the mating period (maximum of 2 menstrual cycles), and during early pregnancy (up to gestation day 25). Increases in blood total IgE levels were observed, but there were no other abnormalities in menstrual cycles, copulation index, fertility index, clinical observations, etc. and the NOAEL was determined to be 75 mg/kg (4.2.3.5.1-2).

In a cynomolgus monkey study for effects on embryo-fetal development by subcutaneous administration, Omalizumab (0, 3, 15, 75 mg/kg) was administered to pregnant females once daily on gestation days 20 to 22 and then once weekly through gestation day 50. Although abortion occurred in 1 of 12 maternal animals each in the control, 3-mg/kg, and 75-mg/kg groups, the changes in clinical observations observed in the animals that aborted were only bleeding around the reproductive organ both in the Omalizumab and control groups, which was a finding observed during early pregnancy also in many animals without abortion. In addition, all the animals exhibited no abnormalities in body weight, food consumption, and laboratory tests. The incidence was comparable to the laboratory background incidence (8%) and the incidences reported in the literature (Small MF, *Am J Primatol.* 1982;2:137-47, Hendrie TA et al., *Am J Primatol.* 1996;40:41-53). Therefore, abortion was judged unrelated to Omalizumab. No fetal abnormalities were observed and there were no abnormalities including changes in clinical observations etc., except for increases in total IgE levels in maternal animals. The NOAELs for maternal animals and for F1 fetuses were both determined to be 75 mg/kg (4.2.3.5.2-1).

In a cynomolgus monkey study for effects on pre- and post-natal development and on placental transfer and milk excretion by subcutaneous administration, Omalizumab 75 mg/kg was administered to two groups of females (Caesarean section group and natural delivery group) once daily on gestation days 120 to 122, and then once weekly through gestation day 150 for the Caesarean section group or through day 28 post-partum for the natural delivery group. No maternal animals died or aborted and

no fetal deaths occurred. There were no abnormalities in clinical observations in either group. Also in F1 offsprings, no deaths occurred and there were no abnormalities in clinical observations. Toxicokinetic measurements were performed. As a result, Omalizumab was detected in amniotic fluid (approximately 3.3% of maternal serum level), milk (approximately 0.15%), fetal serum (approximately 32.9%), and offspring serum (approximately 33.2%). Serum total IgE levels were increased in the Omalizumab group. Maternal animals and F1 fetuses/offspring exhibited no abnormalities and the NOAELs for maternal animals and for F1 fetuses/offspring were both determined to be 75 mg/kg. Placental transfer and milk excretion of Omalizumab were noted (4.2.3.5.3-1).

3.(iii).A.(5) Local tolerance

In order to evaluate the irritation caused by different formulations, rabbit local tolerance studies were performed (4.2.3.6-1 to -4). A single intravenous or subcutaneous dose of 1 mL of Omalizumab [REDACTED] formulation (5 mg/mL), 1 mL of Omalizumab lyophilized formulation (100 mg/mL), or 1.2 mL of Omalizumab lyophilized formulation (125 mg/mL) was administered to rabbits. As a result, there were no macroscopic or histologic findings at the injection site. When Omalizumab [REDACTED] formulation (5 mg/mL) or Omalizumab lyophilized formulation (20 and 40 mg/mL) was subcutaneously administered once daily for 14 days, as compared to animals administered placebo or saline in the same manner, there was a mild increase in the severity of subacute inflammation at the injection site, but no histological changes suggestive of impaired skin function (necrosis or ulcer) were observed.

3.(iii).A.(6) Other toxicity studies

Because thrombocytopenia was observed in the 6-month, subcutaneous toxicity study in juvenile cynomolgus monkeys etc., various studies were conducted to investigate the mechanism of thrombocytopenia.

(a) *In vivo* studies

In rhuMAb E26 subcutaneous toxicity study, rhuMAb E26 (a humanized monoclonal antibody that is similar to Omalizumab, with a higher affinity for IgE than Omalizumab) (0, 4, 10, 40 mg/kg) was administered to adult cynomolgus monkeys once daily on Study Days 1 to 3 and then once weekly for 4 weeks and rhuMAb E26 (0, 40, 200 mg/kg) was administered to juvenile monkeys once weekly for 26 weeks. A trend towards decreased platelet counts was noted in adult monkeys in the 40-mg/kg group and juvenile monkeys exhibited decreased platelet counts and associated prolonged bleeding time and organ bleeding at ≥ 40 mg/kg (4.2.3.7.3-1, 2).

In 4-, 6-, and 26-week subcutaneous toxicity studies in juvenile and adult cynomolgus monkeys, Omalizumab (0, 15, 30, 50, 100, 250 mg/kg) was subcutaneously administered once weekly to juvenile and adult cynomolgus monkeys and the duration of dosing was 26 weeks for the 15-, 30-, and 50-mg/kg groups and 6 weeks for the 100- and 250-mg/kg groups. A 13-week recovery period after 4-week dosing was scheduled for a proportion of control and 250 mg/kg juvenile animals.

Thrombocytopenia occurred in juvenile animals at all dose levels and in adult male animals at ≥ 30 mg/kg and in adult female animals at ≥ 100 mg/kg. Necropsies of juvenile and adult animals treated with 100 and 250 mg/kg for 6 weeks revealed red lesions in the brain, thymus, lung, gastrointestinal tract, heart, and bladder and histopathologic examinations showed focal hemorrhage in these organs and increased megakaryocytes in bone marrow. After a recovery period, the incidence of focal hemorrhage was lowered, but megakaryocytes did not recover completely. When serum total IgE levels were measured, increases in total IgE levels were noted in the Omalizumab groups, but there was no relationship between baseline IgE levels or total IgE levels and thrombocytopenia (4.2.3.7.3-4).

In a study on the effects of an intravenous immunoglobulin preparation on thrombocytopenia, Omalizumab (0 and 100 mg/kg) was subcutaneously administered once weekly for 3 weeks to female juvenile cynomolgus monkeys and an intravenous immunoglobulin preparation (which is considered to bind to Fc γ receptors within the reticuloendothelial system and reduce platelet clearance from the circulation by the reticuloendothelial system) was intravenously administered to a proportion of the animals in the 100 mg/kg group and the control group on Study Days 17 and 18. As a result, while thrombocytopenia occurred in the Omalizumab group, thrombocytopenia recovered when an immunoglobulin preparation was concomitantly used, indicating that Fc γ receptors within the reticuloendothelial system are involved in thrombocytopenia associated with Omalizumab (4.2.3.7.3-5).

In a 4-week subcutaneous toxicity study of rhuMAb 2C4, rhuMAb 2C4 (a humanized monoclonal antibody having the same human IgG1 structure as Omalizumab, but different complementarity-determining regions [CDRs]) 250 mg/kg was administered once weekly to juvenile cynomolgus monkeys. As a result, there were no effects on the number and morphology of platelets, indicating that the CDRs may be involved in thrombocytopenia associated with Omalizumab (4.2.3.7.3-6).

In a 4-week subcutaneous toxicity study in chimpanzees, Omalizumab 250 mg/kg was administered to chimpanzees. As in cynomolgus monkeys, thrombocytopenia associated with increases in bone marrow megakaryocytes was noted, which resolved upon drug withdrawal (4.2.3.7.3-7).

In a 11-week subcutaneous toxicity study in African green monkeys, rhesus monkeys, and cynomolgus monkeys, cynomolgus monkeys in the 100- and 250-mg/kg groups exhibited thrombocytopenia associated with increases in bone marrow megakaryocytes. Although transient thrombocytopenia was found sporadically in African green monkeys and rhesus monkeys at 250 mg/kg, thrombocytopenia did not persist except for 1 of 3 rhesus monkeys and there were also no statistically significant differences. Some of the rhesus monkeys and African green monkeys exhibited increases in megakaryocytes, which were milder than those in cynomolgus monkeys (4.2.3.7.3-8).

(b) *In vitro* studies

In a study for the effects on platelet count and platelet activation, platelet count was measured after Omalizumab was added to human or cynomolgus monkey blood. As a result, there were no effects. When human or cynomolgus monkey platelet-rich plasma was added with Omalizumab and incubated, platelet aggregation was not induced. Also, when human or cynomolgus monkey platelet-rich plasma was added with Omalizumab, incubated and added with thrombin receptor-activating peptide, platelet aggregation was not enhanced (4.2.3.7.3-12).

In hemolysis and blood compatibility testing, 5 to 100 mg/mL of Omalizumab solution was mixed with human or cynomolgus monkey blood, serum, or plasma. As a result, Omalizumab did not cause hemolysis and was compatible with serum and plasma (4.2.3.7.7-1 to -3).

In tissue cross-reactivity studies, the tissue specificity of Omalizumab against cynomolgus monkey tissues and normal human tissues was determined immunohistologically. In cynomolgus monkey tissues, specific reactivities of Omalizumab and MaE11 (Omalizumab's parental murine anti-human IgE monoclonal antibody) were observed with lymph node germinal center and Peyer's patch in the large intestine. In human tissues, specific reactivity of Omalizumab was not observed, but specific reactivity of MaE11 was observed with spleen lymphoid cells (4.2.3.7.7-4 to -5).

Based on the results of the above studies, the applicant explained as follows:

Although the possibility that Omalizumab increases the risk of thrombocytopenia in humans cannot be excluded, (a) in any of the adult cynomolgus monkeys treated with a high-dose of Omalizumab for a long period of time, platelet count was not reduced to $< 50000/\mu\text{L}$ (corresponding to Grade 3 in "Seriousness Classification of Adverse Drug Reactions" [MHW/PAB/SD Notification No. 80 dated June 29, 1992]). (b) According to pharmacodynamic analysis using the data from cynomolgus monkey and chimpanzee toxicity studies, the serum Omalizumab concentration required to attain a 50% drop in platelets from baseline was estimated to be $2430 \mu\text{g/mL}$ in adult animals and $1490 \mu\text{g/mL}$ in juvenile animals while according to population pharmacokinetic analysis using the data from foreign clinical studies, a steady-state C_{max} ($C_{\text{max, ss}}$) of $> 500 \mu\text{g/mL}$ was not observed. (c) Assuming that susceptibility to thrombocytopenia in cynomolgus monkeys and chimpanzees is comparable to that in humans, the effects on platelet count were investigated by pharmacokinetic-pharmacodynamic model analysis based on these C_{max} ($C_{\text{max, ss}}$) values and the data from cynomolgus monkey and chimpanzee toxicity studies. As a result, the presumptive frequency of a platelet count $< 50\%$ of the baseline level or $< 75000/\mu\text{L}$ was calculated to be less than one in 200,000 cases. (d) Based on Japanese and foreign clinical studies, decreases in platelet counts reported as adverse events (Japanese Studies 1303, 1304, and 1307, three subjects in the Omalizumab group; Foreign ALC population,⁵ 2 subjects in the Omalizumab group and 1 subject in the control group [a causal relationship was denied except for 1

⁵ A pooled population from comparative studies in patients with allergic asthma, [REDACTED], and [REDACTED], consisting of 6130 subjects.

Japanese subject with decreased platelet count associated with eosinophilic pneumonia]), the time course of the mean platelet count before and after study drug administration and changes from baseline at final assessment (shift analysis), and the maximum reduction in platelet count observed during the clinical study were analyzed. As a result, there were no differences between the treatment groups. Therefore, the possibility of thrombocytopenia in humans should be very low.

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

3.(iii).B.(1) Thrombocytopenia

PMDA asked the applicant to explain a possible mechanism of development of thrombocytopenia, based on the results of studies on thrombocytopenia associated with Omalizumab.

The applicant explained as follows:

(a) In the 4-week subcutaneous toxicity study with rhuMAb2C4, there were no changes in platelet counts, indicating that the CDRs of Omalizumab may be involved in thrombocytopenia associated with Omalizumab. (b) In immune-mediated thrombocytopenic purpura, the Fc portion of antiplatelet antibodies bound to platelets binds to Fc γ receptors within the reticuloendothelial system, resulting in phagocytosis of platelets, which is considered to be a cause of thrombocytopenia (Miwa et al. *Hematology*. 2nd ed. 1995:1196-1250) and following the administration of an intravenous immunoglobulin preparation, the Fc portion of immunoglobulin blocks Fc γ receptors within the reticuloendothelial system, which inhibits thrombocytopenia (Miwa et al. *Hematology*. 2nd ed. 1995:1196-1250). (c) Thrombocytopenia occurring following the administration of Omalizumab also recovered with an intravenous immunoglobulin preparation. Taking account of these findings, although *in vitro* studies showed no specific interactions between Omalizumab and platelets, it is inferred that platelet clearance from circulation is enhanced because *in vivo* binding to platelets occurs with the involvement of the CDRs of Omalizumab, which leads to binding to Fc γ receptors within the reticuloendothelial system, thereby inducing phagocytosis.

PMDA asked the applicant to explain the latest information on the occurrence of adverse events of thrombocytopenia and haemorrhage from overseas marketing experience and the necessity of including a caution statement about the use in patients with low platelet counts, measurement of platelet counts after the administration of Omalizumab, etc. in the package insert.

The applicant explained as follows:

Using the safety information database of Novartis headquarters (Switzerland), the occurrence of thrombocytopenia collected up to ■■■ 20■■■ from overseas marketing experience was examined. As a result, there were 14 cases with relevant adverse events reported (6 cases from spontaneous reporting, 1 case from the literature, 7 cases from PMS), of which, a causal relationship to the drug was denied for all 7 cases from PMS. Of the remaining 7 cases, 1 case reported as “idiopathic thrombocytopenic purpura” had a platelet count of 0, but for the other 6 cases, no detailed information has been available, such as the time course of platelet count and clinical course. Likewise, the occurrence of haemorrhage

relating to “skin and subcutaneous tissue disorders,” e.g. subcutaneous haemorrhage and ecchymosis, which are general haemorrhage symptoms due to thrombocytopenia, was examined. As a result, there were 24 relevant adverse events reported (19 events from spontaneous reporting, 1 event from the literature, 4 events from PMS). Of which, a causal relationship was denied for all 4 events from PMS. Of the remaining 20 events, decreased platelet count was reported at the onset of a haemorrhagic event in 3 cases only, i.e. 2 events of “petechiae” and 1 event of “increased tendency to bruise” (the same cases as 3 of the 14 cases with thrombocytopenia). Of the other 17 events, there is no information on thrombocytopenia for 14 events and the platelet count at the time of event onset has been reported to be normal for 3 events. At present, there have been no results clearly indicating that Omalizumab may induce thrombocytopenia and “thrombocytopenia” has already been listed in the Other Adverse Reactions section of the proposed package insert. Therefore, it is unnecessary to include an additional caution statement.

PMDA considers as follows:

While there was only 1 case with thrombocytopenia reported from overseas marketing experience at the time of regulatory submission in Japan, the latest information indicates a trend towards its increase. Thus, at least, the package insert should warn that thrombocytopenia has occurred in non-clinical studies. It is also necessary to further investigate the relationship between Omalizumab and thrombocytopenia through post-marketing surveillance by paying an attention to bleeding tendency after the administration of Omalizumab and measuring platelet counts in the event of bleeding tendency.

4. Clinical data

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

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

The results from 2 foreign studies, i.e. bioavailability and bioequivalence studies of Omalizumab (5.3.1.1-1, 5.3.1.2-2) were submitted. During the clinical development of Omalizumab, the drug products with different formulation codes were used and lyophilized powder for injection with formulation codes G158BP, G158CF, and GA158CF were used in Japanese clinical studies.

Omalizumab concentrations in human serum (including both free Omalizumab and Omalizumab-IgE complex) were measured by an ELISA using monoclonal antibodies directed against the complementarity-determining regions (CDRs) of Omalizumab (lower limit of quantification, ■ ng/mL). Serum total IgE concentrations were measured by microbead enzyme immunoassay (lower limit of quantification, ■ ng/mL), and serum free IgE concentrations (lower limit of quantification, ■ ng/mL) and titers of serum anti-Omalizumab antibodies were measured by an ELISA (lower limit of quantification, antibody titer = ■). Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the mean ± SD.

In clinical studies in which Omalizumab was administered subcutaneously or intravenously, no

anti-Omalizumab antibodies were detected.

4.(i).A.(1) Bioavailability (5.3.1.1-1, Study Q0723g [■ 19■ to ■ 19■])

An open-label study in foreign patients with allergic asthma (5 adults each; 5 adolescents each; 13 children each) was conducted to assess pharmacokinetics and pharmacodynamics. Multiple doses of Omalizumab (lyophilized powder for injection [drug concentration, 100 mg/mL]) were administered subcutaneously (0.014 mg/kg/[IU/mL]) or intravenously (0.007 or 0.014 mg/kg/[IU/mL]). In asthma patients, the bioavailability (BA) of Omalizumab after subcutaneous administration relative to intravenous administration was calculated to be 0.66.

4.(i).A.(2) Bioequivalence (5.3.1.2-2, Study 2203 [■ 20■ to ■ 20■])

An open-label, parallel-group, comparative study was conducted in foreign healthy volunteers with a baseline serum IgE level of 30 to 300 IU/mL (83 subjects) to investigate bioequivalence after a manufacturing site change. Following a single subcutaneous dose of the formulation codes G158BP and G158CF (the drug concentration was 125 mg/mL for both), the 90% confidence intervals for the mean ratios of AUC and C_{max} (G158CF/G158BP) were 0.81 to 1.06 and 0.83 to 1.09, respectively, and the pre-change and post-change formulations were determined to be bioequivalent. The mean time to reach the minimum level of serum free IgE was 3.15 days (G158BP) and 3.24 days (G158CF) and the mean percent reduction was 95% for both formulations.

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the pharmacokinetic data from a Japanese single subcutaneous dose study in Japanese healthy volunteers (5.3.3.1-1), a Japanese clinical study in patients with bronchial asthma (5.3.5.1-1), and a clinical study comparing pharmacokinetics and pharmacodynamics between Japanese and Caucasian (foreign) healthy volunteers (5.3.3.3-1) were submitted. As the reference data, the results from 2 Japanese studies in patients with seasonal allergic rhinitis (5.3.5.4-2, 5.3.5.4-3) and 15 foreign clinical studies were submitted.

In foreign countries, the dosage and dose regimen for Omalizumab has been established based on the mode of action and pharmacodynamic properties of Omalizumab, instead of an investigation of dose-clinical response at fixed doses, which is generally conducted. Also, in Japan, no dose-finding study has been conducted and the dosage and dose regimen similar to that in foreign countries is used. Thus, their appropriateness has been determined by comparing pharmacokinetics and pharmacodynamics between Japanese and foreign subjects.

4.(ii).A.(1) Studies in healthy volunteers

(a) Japanese single subcutaneous dose study (5.3.3.1-1, CIGE0251101 [Study 1101] [■ 19■ to ■ 20■])

A single-blind, parallel-group, placebo-controlled, comparative study in Japanese healthy male

volunteers (12 subjects per group) was conducted to assess the pharmacokinetics and pharmacodynamics of Omalizumab. The pharmacokinetic parameters of Omalizumab following single subcutaneous doses of 75, 150, 300, and 375 mg are presented in the following table and the AUC increased with increasing dose and the $t_{1/2}$ was almost constant regardless of the dose.

Serum free IgE and total IgE levels, which were measured at the same time, are shown in the table below. Free IgE levels decreased with increasing serum Omalizumab levels and reached the minimum levels at 2 to 4 days post-dose. The duration of free IgE levels ≤ 25 ng/mL (the target serum free IgE level associated with clinical benefit; see 4.(ii).A.(4) below) tended to be prolonged with increasing dose and serum total IgE levels rose as serum Omalizumab levels increased.

Table. PK parameters following a single subcutaneous dose of Omalizumab in Japanese healthy volunteers

| Dose (mg) | t_{max} (day) | C_{max} ($\mu\text{g/mL}$) | AUC ($\text{day} \cdot \mu\text{g/mL}$) | CL/F (mL/day/kg) | Vz/F (mL/kg) | $t_{1/2}$ (day) |
|-----------|-----------------|--------------------------------|---|-----------------------------|-------------------------|-----------------|
| 75 | 9 | 12.6 ± 1.3 | 434 ± 129 | 3.00 ± 0.65 | 71.6 ± 7.3 | 17.1 ± 3.7 |
| | [4-14] | [9.9, 14.9] | [266, 768] | [1.69, 3.81] | [60.3, 85.3] | [14.1, 26.6] |
| 150 | 9 | 24.4 ± 2.7 | 767 ± 80 | 3.01 ± 0.35 | 73.7 ± 7.8 | 17.1 ± 2.2 |
| | [4-14] | [20.3, 28.7] | [636, 932] | [2.43, 3.66] | [61.5, 87.4] | [14.1, 22.1] |
| 300 | 7 | 43.6 ± 9.6 | 1633 ± 415 | 3.19 ± 0.67 | 82.9 ± 19.4 | 18.4 ± 4.2 |
| | [4-10] | [32.6, 64.8] | [1085, 2264] | [2.05, 4.36] | [58.2, 123.1] | [11.5, 22.9] |
| 375 | 4 | 60.0 ± 8.1 | 2268 ± 667 | 2.90 ± 0.82 | 80.1 ± 13.0 | 20.4 ± 6.2 |
| | [4-14] | [39.9, 68.7] | [1361, 3427] | [1.82, 4.67] | [66.1, 107.1] | [13.2, 24.1] |

Mean \pm SD [Min, Max], t_{max} is median [range] (n = 12)

Table. Serum free IgE and total IgE parameters following a single subcutaneous dose of Omalizumab in Japanese healthy volunteers

| Dose (mg) | Baseline total IgE level (IU/mL) | N | Free IgE | | Total IgE | | |
|-----------|----------------------------------|----|-----------------------------|-----------------------------------|--------------------------------|--|-----------------------------------|
| | | | Minimum serum level (ng/mL) | Time to reach minimum level (day) | Maximum serum level (ng/mL) | Ratio of maximum level to baseline level | Time to reach maximum level (day) |
| 75 | ≤ 150 | 3 | 19.67 [16.1-22.9] | 4 [2-4] | 1657 ± 496 [1317-2226] | 6.3 [4.7-6.3] | 14 [10-42] |
| | ≥ 151 | 9 | 39.14 [17.0-65.4] | 4 [2-7] | 3285 ± 1007 [1956-5167] | 4.3 [2.0-6.3] | 14 [1-28] |
| 150 | ≤ 150 | 1 | 6.8 [-] | - [2] | 1435 [-] | 4.5 [-] | 28 [-] |
| | ≥ 151 | 11 | 19.93 [9.3-33.3] | 2 [1-10] | 4220 ± 1430 [2327-7191] | 4 [2.8-5.6] | 10 [7-56] |
| 300 | ≤ 150 | 1 | 9.45 [-] | - [2] | 1974 [-] | 7.9 [-] | 42 [-] |
| | ≥ 151 | 11 | 14.64 [8.7-28.2] | 2 [2-4] | 3694 ± 916 [2609-4995] | 4.7 [2.6-7.3] | 28 [10-42] |
| 375 | ≤ 150 | 4 | 4.75 [3.7-5.9] | 3 [2-4] | 2070 ± 634 [1565-2945] | 7.5 [6.1-9.9] | 42 [10-70] |
| | ≥ 151 | 8 | 9.97 [5.7-16.9] | 3 [2-4] | 3739 ± 1189 [2475-5930] | 4.8 [3.1-5.3] | 14 [10-42] |

Mean \pm SD or Mean [range], t_{min} and t_{max} are median. -: Not calculated.

(b) Comparison of pharmacokinetics and pharmacodynamics between Japanese and foreign healthy volunteers (5.3.3.3-1, CIGE025A2206 [Study 2206] [20 to 20])

An open-label, uncontrolled, parallel-group, comparative study in Japanese and foreign healthy male volunteers who have similar baseline serum IgE level and body weight (19 subjects each) was conducted to compare the pharmacokinetics and the effects on serum free IgE between the Japanese and foreign subjects (body weight, Japanese subjects, 60.54 ± 5.44 [50.5-69.8] kg, foreign subjects, 61.63 ± 5.31 [53.3-69.5] kg; baseline serum IgE, Japanese subjects, 69.7 ± 23.3 [32-96] IU/mL, foreign subjects, 48.4 ± 12.5 [32-73] IU/mL, Mean \pm SD [range]).

The pharmacokinetic parameters, serum free IgE levels, and serum total IgE levels following a single subcutaneous dose of 150 mg of Omalizumab are shown in the following table.

Serum Omalizumab concentrations reached C_{max} at 2 to 10 days post-dose and the terminal elimination phase half life was calculated to be 21 to 25.5 days. The C_{max} in Japanese subjects was 17% higher than in foreign subjects. On the other hand, the AUC was similar between the two racial groups. Serum free IgE levels reached the minimum levels at 24 to 48 hours post-dose and then slowly returned to near baseline levels with decreasing serum Omalizumab levels. Serum total IgE levels tended to slowly increase and reach the maximum levels at 28 days post-dose before declining.

Table. PK parameters following a single subcutaneous dose of Omalizumab in foreign and Japanese subjects

| | t_{max} (day) | C_{max} (ng/mL) | AUC (day· μ g/mL) | $t_{1/2}$ (day) | V_z/F (L) | CL/F (mL/day) |
|-------------------|--------------------|----------------------|--------------------------|--------------------|-----------------|------------------|
| Foreign subjects | 7 [3, 10] | 14200 \pm 1920 | 673 \pm 86.3 | 25.5 \pm 3.99 | 8.22 \pm 1.12 | 226 \pm 28.1 |
| Japanese subjects | 7 [2, 14] | 16700 \pm 2730 | 642 \pm 134 | 21.0 \pm 3.49 | 7.25 \pm 1.33 | 242 \pm 45.4 |

Dose, 150 mg, Mean \pm SD, t_{max} is median [Min, Max], (n = 19)

Table. Serum free IgE and total IgE levels following a single subcutaneous dose of Omalizumab

| | Free IgE | | | Total IgE | | |
|-------------------|--------------------------------|-------------------------|---------------------------------|--------------------------------|-------------------------|-----------------------------------|
| | Minimum serum level (ng/mL) | Percent decrease (%) | Time to reach minimum level (h) | Maximum serum level (ng/mL) | Percent increase (%) | Time to reach maximum level (day) |
| Foreign subjects | 5.92 \pm 2.72 | 94.8 \pm 2.4 | 24 [12-168] | 810.5 \pm 224.6 | 713.8 \pm 263.1 | 28 [10-56] |
| Japanese subjects | 7.48 \pm 5.62 | 95.4 \pm 2.8 | 48 [24-72] | 1107.2 \pm 348.0 | 585.8 \pm 183.7 | 28 [14-56] |

Dose, 150 mg, Mean \pm SD, Time to reach minimum level and time to reach maximum level are median [range] (n = 19)

4.(ii).A.(2) Investigation of pharmacokinetics and pharmacodynamics in Japanese patients with allergic bronchial asthma (5.3.5.1-1, CIGE025A1304 [Study 1304] [February 2003 to May 2005])

The pharmacokinetics of Omalizumab was investigated in a randomized, double-blind, parallel-group, placebo-controlled, comparative study in Japanese patients with moderate to severe allergic asthma. Following multiple subcutaneous doses of 150, 225, 300, and 375 mg of Omalizumab every 2 or 4 weeks (the dose and dosing frequency were determined based on each patient's baseline serum IgE level and body weight according to the dosing charts), serum Omalizumab trough concentrations at 16 weeks after the first dose were 1.5- to 1.8-fold those at 4 weeks. At 16 weeks, serum free IgE levels were reduced to \leq 25 ng/mL in most patients regardless of the dose level or dosing frequency and returned to near baseline levels in the follow-up phase after multiple-dose administration (at 24 or 26 weeks). Serum free IgE levels were reduced by between 89.8% and 99.0% at 16 weeks compared to the baseline levels, regardless of the dose level or dosing frequency. Serum total IgE levels at 16 weeks were 2.7- to 5.0-fold higher than the baseline levels, but tended to decline in the follow-up phase after the end of administration, as compared to those at 16 weeks.

Similar results have been obtained also from Japanese clinical studies in patients with seasonal allergic rhinitis (Studies 1303 [5.3.5.4-2] and 1305 [5.3.5.4-4]).

4.(ii).A.(3) Population pharmacokinetic-pharmacodynamic analysis (5.3.3.5-4)

Using the data on serum Omalizumab, free IgE, and total IgE concentrations obtained from Study 1101 in Japanese healthy volunteers and Study 1305 in Japanese seasonal allergic rhinitis patients (202 subjects, 3192 sampling points), population pharmacokinetic-pharmacodynamic analysis by NONMEM (Version V Level 1.1, ADVAN6, FOCE) was performed, assuming a 1-compartment model with 1st order absorption. In building the model, the influences of background factors were evaluated (baseline serum IgE level, body weight, age, and gender; likelihood ratio test, $P < 0.01$) and baseline serum IgE level and body weight were identified as factors affecting the pharmacokinetics-pharmacodynamics of Omalizumab.

Population pharmacokinetic-pharmacodynamic parameters in the final model (population mean [inter-individual variability, %CV]) were as follows: absorption rate constant (k_a), 0.0200 h^{-1} (39.9%); endogenous production rate of IgE (PE/f), $30.3 \text{ } \mu\text{g/h}$ (23.1%); clearance of serum free Omalizumab (CL_X/f), 7.32 mL/h (20.3%); clearance of serum free IgE (CL_E/f), 71.0 mL/h (25.3%); the difference between clearances of serum complex and free Omalizumab ($\Delta CL_C/f$), 5.86 mL/h (34.9%); distribution volume of serum free Omalizumab (V_X/f) = distribution volume of serum free IgE (V_E/f), 5900 mL (13.0%); and distribution volume of serum Omalizumab-IgE complex (V_C/f), 3630 mL (25.0%). The intra-individual variabilities for serum Omalizumab, total IgE, and free IgE (%CV) were 16.7%, 21.1%, and 21.8%, respectively.

In order to evaluate the effects of race, a simulation based on the final model was performed using the patient background in Foreign Studies 007, 008, and 009. As a result, at all dosage regimens in the Omalizumab group, the observed values for serum free IgE, total IgE, and Omalizumab trough concentrations showed similar distributions to those of the predicted values. Also when a similar simulation was performed based on the patient background in Study 1304 involving Japanese allergic bronchial asthma patients in order to evaluate the effects of pathological condition, the predicted values for serum free IgE, total IgE, and Omalizumab trough concentrations almost agreed with the observed values.

4.(ii).A.(4) The appropriateness of the overseas dosage and dose regimen and dosing charts adopted for the use in Japan

In foreign countries, the dosage and dose regimen for Omalizumab was selected by exploring for the target serum free IgE level associated with clinical benefit and assessing the doses of Omalizumab required to maintain this target level. Namely, in foreign clinical studies (Studies Q0694g and 006), Omalizumab showed efficacy when administered intravenously at $0.006 \text{ mg/kg/[IU/mL]}$ every 2 weeks or subcutaneously at 300 mg every 3 or 4 weeks and the median steady-state serum free IgE levels were $16 \text{ to } 30 \text{ ng/mL}$. Also in another foreign phase II clinical study, the mean serum free IgE level associated with clinical benefit of Omalizumab was $< 28 \text{ ng/mL}$. Therefore, $\leq 25 \text{ ng/mL}$ was chosen as the target serum free IgE level that is expected to be associated with the efficacy of Omalizumab and $0.008 \text{ mg/kg/[IU/mL]}$ subcutaneously administered every 2 weeks or 0.016

mg/kg/[IU/mL] subcutaneously administered every 4 weeks was selected as the recommended clinical dose of Omalizumab to maintain a mean serum free IgE level of ≤ 25 ng/mL. The doses for individual patients need to be calculated based on the baseline serum total IgE level and body weight, which is complicated. Therefore, dosing charts (see the following tables) were developed and used in clinical studies.⁶

Table. Dosing charts proposed for this application (at the time of filing) and used in the US post-marketing experience

Administration Every 4 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | |
|--|------------------|------------------------------|---------|---------|----------|
| | 30-60 | > 60-70 | > 70-80 | > 80-90 | > 90-150 |
| ≥ 30 -100 | 150 mg | 150 mg | 150 mg | 150 mg | 300 mg |
| > 100-200 | 300 mg | 300 mg | 300 mg | 300 mg | |
| > 200-300 | 300 mg | Administration every 2 weeks | | | |

Administration Every 2 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | |
|--|------------------------------|---------|---------|---------|-------------|
| | 30-60 | > 60-70 | > 70-80 | > 80-90 | > 90-150 |
| ≥ 30 -100 | Administration every 4 weeks | | | | |
| > 100-200 | | | | | 225 mg |
| > 200-300 | 225 mg | | 225 mg | 225 mg | 300 mg |
| > 300-400 | 225 mg | 225 mg | 300 mg | 300 mg | Do not dose |
| > 400-500 | 300 mg | 300 mg | 375 mg | 375 mg | |
| > 500-600 | 300 mg | 375 mg | | | |
| > 600-700 | 375 mg | | | | |

In Study 2206, the pharmacokinetics and pharmacodynamics of Omalizumab were almost comparable between Japanese and foreign healthy male volunteers with similar baseline serum IgE level and body weight and it was shown that race does not significantly affect the pharmacokinetics and pharmacodynamics of Omalizumab, except for these two background factors. Assessments using a population pharmacokinetic-pharmacodynamic model based on the mode of action confirmed that the pharmacokinetics of Omalizumab, free IgE, and Omalizumab-IgE complex are influenced by baseline serum IgE level and body weight, but are not significantly affected by race or pathological condition. In Japanese clinical studies conducted actually using the dosing charts, serum free IgE levels were kept below 25 ng/mL. Therefore, the applicant concluded that it is appropriate to determine a dosage and dose regimen for Japanese allergic asthma patients in accordance with the dosing charts that are similar to those used overseas.

Since serum total IgE levels are elevated following administration of Omalizumab, the package insert will include a caution statement that re-testing of serum IgE levels during Omalizumab treatment should not be used to reassess the dosage and dose regimen.

⁶ These dosing charts were used in Foreign Studies 008 and 009, Japanese Study 1304, etc. In Foreign Study 2306 etc., dosing charts with subdivision of the body weight categories of ≤ 60 kg and > 90 kg were used and the current Company Core Data Sheet (CCDS) contains further modified dosing charts [see 4.(iii).B.(3).1 Justification for dose determination method].

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

4.(ii).B.(1) Comparison of pharmacokinetics between Japanese and foreign subjects

PMDA asked the applicant to discuss the cause of a significant difference in the C_{max} of Omalizumab between Japanese and foreign subjects and higher serum Omalizumab concentrations in Japanese subjects than in foreign subjects in Study 2206.

The applicant explained as follows:

In Study 2206, the subject background (age, body weight, height, BMI) was similar between Japanese and foreign subjects and a difference in the mean C_{max} value of Omalizumab between the two races is not considered attributable to the subject background. On the other hand, the mean baseline IgE level was 48.4 IU/mL in foreign subjects as compared to 69.7 IU/mL in Japanese subjects. Although no clear correlation between baseline serum IgE level and the C_{max} value of Omalizumab was found, 2 Japanese subjects with the highest baseline IgE level showed the highest C_{max} value of Omalizumab and differences in IgE level may have affected the C_{max} . Because it is considered important to confirm the effect of Omalizumab based on a decrease in free IgE level, the percent decrease in serum IgE level was compared. As a result, the percent decreases in the two races were both about 95% within about 2 days post-dose, and the serum free IgE concentration-time curve up to 56 days post-dose was similar between Japanese and foreign subjects.

Although the cause of a difference in the C_{max} of Omalizumab between Japanese and foreign subjects observed in Study 2206 is unclear, considering that its impact on the efficacy and safety of Omalizumab is small, PMDA accepted the applicant's response.

4.(ii).B.(2) The relationship between the pharmacokinetics of Omalizumab and its effects on free IgE

PMDA asked the applicant to discuss the reason why the time to reach the minimum level of serum free IgE is 3 to 5 days, which is shorter compared to the t_{max} of Omalizumab (9 days).

The applicant explained as follows:

In Study 1101, at 4 to 10 days after the administration of Omalizumab, serum Omalizumab levels were almost maintained at near C_{max} and serum free IgE levels were almost constant at near the minimum level. Thus, there should be no major temporal gap between the pharmacokinetics of Omalizumab and its effects on free IgE. The relationship between serum Omalizumab levels and serum free IgE levels until the maximum serum level was reached after the administration of Omalizumab was plotted for each subject. As a result, some variability was observed at a dose of 75 mg of Omalizumab, but at doses of 150, 300, and 375 mg of Omalizumab, when serum Omalizumab levels reached 10 to 30 $\mu\text{g/mL}$, serum IgE levels reached the minimum level in many subjects and at higher serum Omalizumab levels, serum free IgE levels were almost constant at near the minimum level. At doses other than 75 mg, serum Omalizumab levels in many subjects reached $\geq 10 \mu\text{g/mL}$ at 1 to 4 days after the administration of Omalizumab. Therefore, it is considered that serum free IgE levels reach the

minimum level when serum Omalizumab levels are increased to about 10 µg/mL or higher, and even when serum Omalizumab levels further rise, serum free IgE levels are almost maintained at the minimum level, resulting in a gap between the time to reach the minimum level of serum free IgE and the time to reach the maximum level of serum Omalizumab.

PMDA accepted the above response.

4.(ii).B.(3) Anti-Omalizumab antibody formation

No anti-Omalizumab antibodies have been detected except for 1 subject who inhaled the aerosolized formulation in the early phase of development. PMDA asked the applicant to explain whether it was possible to appropriately measure anti-Omalizumab antibodies in the presence of Omalizumab in blood by an ELISA used in clinical studies and then explain the reason for a low incidence of antibody formation with Omalizumab.

The applicant explained as follows:

It has been confirmed that the ELISA used for measurement of anti-Omalizumab antibody in clinical studies can detect antibodies even in the presence of up to ■■■ µg/mL of Omalizumab in serum. For measurement of anti-Omalizumab antibody, serum samples obtained beyond 12 weeks after the last dose of Omalizumab were used. At this time point, serum Omalizumab concentrations in most samples were as low as ≤ ■■■ µg/mL. Therefore, it is considered that there was no problem with the antibody assay method. In addition, Omalizumab is produced by humanization of MaE11, a murine anti-human IgE monoclonal antibody. It has a basic structure of human IgG1 constant and framework regions, containing only 5.4% murine residues as the CDRs derived from the murine anti-human IgE monoclonal antibody. Consequently, Omalizumab is unlikely to be recognized as a foreign protein and the incidence of anti-Omalizumab antibody formation should be low. On the other hand, like Omalizumab, trastuzumab is a humanized antibody in which only the CDRs are derived from murine protein, but the development of anti-trastuzumab antibodies (1 of 921 patients) has been reported. Therefore, it cannot be concluded at present whether the incidence of antibody formation with Omalizumab is lower compared to other humanized antibodies.

PMDA accepted the above response. Although no anti-Omalizumab antibodies have been detected in the clinical studies conducted, after the market launch, it is also necessary to assess antibody formation in patients with anaphylaxis [see “4.(ii).B *Outline of the review by PMDA*” for anaphylaxis].

4.(ii).B.(4) Drug-drug interactions

PMDA asked the applicant to explain the effects of concomitant use of other antiasthmatic drugs on the safety and efficacy of Omalizumab based on the clinical study results and overseas post-marketing data.

The applicant explained as follows:

Population pharmacokinetic analysis was performed using the data on serum Omalizumab concentrations obtained from Foreign Studies 008, 009, and 010 in asthma patients and Foreign Studies 006 and 007 in patients with seasonal allergic rhinitis (1397 subjects, 8176 sampling points), and the effect of concomitant drugs on the pharmacokinetics of Omalizumab was evaluated by including concomitant drugs as a covariate. As a result, there was little effect of 36 different concomitant drugs including 20 different antiasthmatic or antiallergic drugs (loratadine, fexofenadine hydrochloride, ibuprofen, etc.) on the apparent clearance of Omalizumab, which suggested that there are no pharmacokinetic drug interactions between concomitant drugs and Omalizumab. In addition, using the safety information database including clinical studies and spontaneous reports, the occurrence of adverse events related to drug-drug interactions was investigated. As a result, adverse events following the concomitant use of zonisamide, zolpidem tartrate, or warfarin with Omalizumab have been reported, but the details (whether these adverse events are caused by drug-drug interactions) are unknown at present.

PMDA accepted the above response, but considers that the effects of concomitant drugs on the safety and efficacy of Omalizumab need to be further assessed through post-marketing surveillance.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from 2 Japanese studies in patients with bronchial asthma (5.3.5.1-1, 5.3.5.2-1-1) were submitted. As the safety evaluation data, the results from 1 Japanese study in healthy volunteers (5.3.3.1-1) and 3 studies in patients with seasonal allergic rhinitis (5.3.5.4-2, 5.3.5.4-3, 5.3.5.4-4) were submitted. As the reference data, the results from 1 prematurely terminated Japanese study in patients with bronchial asthma (5.3.5.4-1) were submitted. In addition, as the efficacy and safety evaluation data, the results from 5 foreign studies in patients with allergic asthma (5.3.5.1-2, 5.3.5.1-3, 5.3.5.1-4, 5.3.5.1-9, 5.3.5.1-12) and as the reference data, the results from 15 foreign controlled studies (5.3.5.1-5 etc.) and 11 foreign uncontrolled studies in patients with allergic asthma, etc. were submitted.

4.(iii).A.(1) Japanese clinical study in healthy volunteers

4.(iii).A.(1).1 Healthy subject PK and initial tolerability study (5.3.3.1-1, CIGE0251101 [■ 19■ to ■ 20■])

A single-blind, placebo-controlled, single dose study in Japanese healthy male volunteers (target number of subjects of 72 [12 subjects each in the Omalizumab groups, 24 subjects in the placebo group]) was conducted to evaluate the tolerability and pharmacokinetics of a single dose of Omalizumab [see “4.(ii) Summary of clinical pharmacology studies” for pharmacokinetics].

Single subcutaneous doses of 75, 150, 300, and 375 mg of Omalizumab or placebo were to be administered.

All of the 72 treated subjects (48 subjects in the Omalizumab groups, 24 subjects in the placebo group) were included in the safety analysis.

Adverse events (excluding abnormal laboratory changes) were observed in 37.5% of the Omalizumab groups (18 of 48 subjects, 60 events) and 45.8% of the placebo group (11 of 24 subjects, 40 events). Laboratory test abnormalities were noted in 81.3% of the Omalizumab groups (39 of 48 subjects, 86 events) and 79.2% of the placebo group (19 of 24 subjects, 44 events). There were no deaths. One subject in the 75 mg group had serious adverse events of rash/pruritus and their causal relationship to Omalizumab could not be denied, but the outcome was reported as “improved.”

Adverse events (including laboratory test abnormalities) for which a causal relationship to the study drug could not be denied (adverse drug reactions) were reported in 14.6% of the Omalizumab groups (7 of 48 subjects) and 12.5% of the placebo group (3 of 24 subjects) and the main events were dermatitis NOS and pruritus NOS (3 cases each) in the Omalizumab groups and queasy etc. (one case each) in the placebo group.

Based on the above results, the applicant explained that the tolerability of a single dose of Omalizumab was demonstrated.

4.(iii).A.(2) Japanese clinical studies in patients with bronchial asthma

4.(iii).A.(2).1 Clinical study in patients with moderate to severe bronchial asthma (5.3.5.4-1, CIGE025A1301 [■■ 20■■ to ■■ 20■■]) (Reference data)

This study was planned as a bridging study that would allow extrapolation of the results from the US confirmatory study, i.e. Study 008 and was conducted as a randomized, double-blind, parallel-group, placebo-controlled, comparative study in bronchial asthma patients receiving treatment with inhaled corticosteroids (beclomethasone dipropionate (BDP) \geq 400 $\mu\text{g}/\text{day}$ or equivalent) and short-acting inhaled β_2 -agonists (target number of subjects of 300 [150 subjects per group]), using the rate of asthma exacerbations as the primary endpoint. However, the permitted concomitant drugs were limited for the severity of the disease in study subjects and the protocol was unsuitable for the medical practice in Japan. Consequently, patient enrollment was slow and the study was prematurely terminated. The study drug was administered to 3 subjects (1 subject in the Omalizumab group, 2 subjects in the placebo group) and there were no particular safety concerns.

Taking account of the outcome of this study, a new confirmatory study, Study 1304, was intended to reflect the medical practice in Japan and include patients who respond inadequately to the best available therapy in Japan, in view of the situation in Europe. The study population was defined as “patients whose asthma symptoms are not controlled by high-dose inhaled corticosteroids (BDP \geq 800 $\mu\text{g}/\text{day}$ or equivalent) plus at least 1 antiasthmatic drug or oral corticosteroids,” which was considered to be the best available therapy in Japan based on the revised version of Adult Asthma Prevention and Management Guidelines (JGL) 1998 and treatment practice etc. at that time. On the other hand, the

rate of asthma exacerbations was expected to be lower in these patients on better therapy as compared to the patient population in Study 1301. In the case of the rate of asthma exacerbations chosen as the primary endpoint, it was estimated that the study would require ■■■ to ■■■ subjects to be analyzed to detect a difference from placebo and ■■■ subjects to be screened, but it seemed very difficult to collect those subjects in Japan alone. Therefore, it was decided to change the primary endpoint to “morning peak expiratory flow (PEF),” which is commonly used for efficacy evaluation for antiasthmatic drugs.

4.(iii).A.(2).2) Clinical study in patients with moderate to severe bronchial asthma (Study 1304) (5.3.5.1-1, CIGE025A1304 [February 2003 to May 2005])

(a) Study results from the overall population

A randomized, double-blind, parallel-group, placebo-controlled, comparative study in patients with moderate persistent to severe persistent allergic bronchial asthma⁷ inadequately controlled with conventional therapies⁸ (target number of subjects of 280 [140 subjects per group]) was conducted to evaluate the efficacy and safety of Omalizumab.

In accordance with the dosing charts used in Foreign Study 008 etc., Omalizumab or placebo was to be subcutaneously administered every 4 or 2 weeks and the duration of treatment was 16 weeks.

All of the 315 treated subjects (151 subjects in the Omalizumab group, 164 subjects in the placebo group) were included in the safety analysis and in the Full Analysis Set (FAS) for efficacy and 296 subjects (143 subjects in the Omalizumab group, 153 subjects in the placebo group) excluding 19 subjects with protocol deviations etc. (8 subjects in the Omalizumab group, 11 subjects in the placebo group) were included in the Per Protocol Set (PPS) for efficacy.

The primary efficacy endpoint of morning PEF in the FAS (baseline values and values at final assessment) and the primary assessment variable of the mean change from baseline at final assessment (LSMean) are shown in the following table. The difference in the mean change between the Omalizumab and placebo groups and its 95% confidence interval were 13.19 L/min [5.93, 20.46], demonstrating a significant difference between the groups ($P < 0.001$, ANCOVA including treatment group, dosing frequency, and baseline value as covariates).

⁷ Patients who have been diagnosed with moderate persistent (step 3) or severe persistent (step 4) asthma based on “Adult Asthma Prevention and Management Guidelines (JGL1998 revised version)” and have a duration of bronchial asthma of at least 1 year.

⁸ Patients inadequately controlled despite inhaled corticosteroids ($BDP \geq 800 \mu\text{g}/\text{day}$) plus at least 1 other therapeutic drug for asthma management

Table. Morning PEF in Study 1304

| | Omalizumab group (N = 151) | Placebo group (N = 164) |
|--|-------------------------------|----------------------------|
| Baseline value ¹ (Mean ± SD) | 323.0 ± 101.17 | 328.0 ± 105.05 |
| Value at final assessment ² (Mean ± SD) | 338.7 ± 101.90 | 330.3 ± 106.55 |
| Mean change ³ [95% CI] | 15.45 [10.21, 20.69] | 2.25 [-2.80, 7.31] |

L/min

1 Mean of the 14 days prior to the start of study drug administration including a morning PEF measurement on the day of the first dose

2 Mean of the 14 days prior to the last observation day for subjects who completed the study treatment phase or mean of the 14 days prior to the last documented measurement for subjects who were withdrawn from the study during the study treatment period

3 LSMean calculated from an ANCOVA model including treatment group, dosing frequency, and baseline value as covariates

The secondary endpoint of the mean change in evening PEF from baseline at final assessment (LSMean) was 12.80 L/min in the Omalizumab group vs. 4.97 L/min in the placebo group, and the between-treatment difference and its 95% confidence interval were 7.83 L/min [0.49, 15.16], demonstrating a significant difference between the groups ($P = 0.037$, ANCOVA including treatment group, dosing frequency, and baseline value as covariates). The mean changes in FEV_{1.0} and %FEV_{1.0} from baseline at Week 16 or at withdrawal (LSMean) were significantly greater in the Omalizumab group (FEV_{1.0}, 39 mL vs. -24 mL [$P = 0.032$]; %FEV_{1.0}, 1.54% vs. -1.23% [$P = 0.011$]; ANCOVA including treatment group, dosing frequency, gender, and baseline value as covariates). With respect to the use of rescue medication (short-acting inhaled β_2 -agonists), symptom score, activities of daily living score, nighttime sleep score, and asthma score during Week 16 or 1 week at withdrawal vs. baseline, there were no significant differences between the groups.

Concerning exploratory endpoints, 6 of 151 subjects (4.0%) in the Omalizumab group and 18 of 164 subjects (11.0%) in the placebo group discontinued the study treatment due to asthma exacerbations⁹ and the risk of experiencing asthma exacerbations was significantly lower in the Omalizumab group (odds ratio and its 95% confidence interval, 0.32 [0.12, 0.83]; $P = 0.019$; logistic regression analysis including treatment group, dosing frequency, and the presence or absence of a history of hospitalization due to asthma exacerbations or emergency room visit for asthma treatment within 1 year prior to obtaining consent as covariates) and an analysis taking account of the time to asthma exacerbation also showed that the risk of experiencing asthma exacerbations was significantly lower in the Omalizumab group (hazard ratio and its 95% confidence interval, 0.32 [0.13, 0.82]; $P = 0.018$; Cox proportional hazards model including treatment group, dosing frequency, and the presence or absence of a history of hospitalization due to asthma exacerbations or emergency room visit for asthma treatment within 1 year prior to obtaining consent as covariates). The number of subjects who had at least 1 asthma worsening week¹⁰ during the study treatment period was 35 of 151 subjects (23.2%) in the Omalizumab group and 55 of 164 subjects (33.5%) in the placebo group. When the frequency distribution of total number of asthma worsening weeks during the study treatment period was compared between the treatment groups, the Omalizumab group had significantly fewer asthma worsening weeks ($P = 0.015$, Cochran-Mantel-Haenszel test adjusted for dosing frequency).

⁹ An asthma exacerbation was defined as addition of corticosteroid therapy or change of antiasthmatic drugs.

¹⁰ Asthma worsening week was defined as a week when the subject experienced either severe, moderate, or mild attack.

Adverse events (including abnormal laboratory changes) occurred in 90.1% of the Omalizumab group (136 of 151 subjects) and 86.6% of the placebo group (142 of 164 subjects). There were no deaths. Serious adverse events were reported by 6 subjects (6 events) in the Omalizumab group (enterocolitis, pneumonia NOS, diabetes mellitus NOS, benign mediastinal neoplasm NOS, prostatitis, asthma NOS [one event each]) and 11 subjects (14 events) in the placebo group (asthma NOS [4 events]; bacterial pneumonia NOS and pneumonia NOS [2 events]; pulmonary tuberculosis and bronchial tuberculosis [2 events]; gastroenteritis NOS; gastric cancer NOS; pain NOS; atrophic gastritis; pleurisy; conversion disorder [one event each]). Although a causal relationship to Omalizumab could not be denied for pneumonia NOS in the Omalizumab group, the outcomes were all reported as “resolved.” Adverse events leading to treatment discontinuation were observed in 4 subjects of the Omalizumab group (platelet count decreased, dermatitis NOS, hepatic dysfunction NOS, urticaria NOS [one case each]) and 4 subjects of the placebo group (hepatic function abnormal NOS [2 cases]; rash NOS and chest discomfort; urticaria NOS [one case each]).

Adverse drug reactions (including abnormal laboratory changes) were reported in 48.3% of the Omalizumab group (73 of 151 subjects) and 38.4% of the placebo group (63 of 164 subjects) and the main events were as shown in the following table.

Table. Main adverse drug reactions in the overall population from Study 1304

| Name of event | Omalizumab group n = 151 | Placebo group n = 164 |
|----------------------------|-----------------------------|--------------------------|
| Injection site erythema | 34 (22.5) | 15 (9.1) |
| Injection site pruritus | 17 (11.3) | 9 (5.5) |
| Injection site swelling | 11 (7.3) | 9 (5.5) |
| Injection site warmth | 10 (6.6) | 8 (4.9) |
| Injection site pain | 9 (6.0) | 10 (6.1) |
| Injection site induration | 8 (5.3) | 4 (2.4) |
| Injection site haemorrhage | 7 (4.6) | 10 (6.1) |
| Immunology NOS abnormal | 11 (7.3) | 12 (7.3) |

Based on the above results, the applicant explained that the efficacy and safety of Omalizumab as add-on therapy were demonstrated in patients with moderate to severe asthma inadequately controlled with standard asthma treatment.

(b) Study results from the target population (a subgroup of patients in the claimed indication)

At the time of initiating Study 1304, “patients treated with high-dose inhaled corticosteroids (BDP \geq 800 μ g/day or equivalent) plus at least 1 antiasthmatic drug or oral corticosteroids” were considered to be those receiving the best available therapy. However, taking account of the subsequent widespread use of novel antiasthmatic drugs e.g. long-acting inhaled β_2 -agonists in Japan and evolution of guidance for medication therapy due to the revision of the JGL, it was considered necessary to further narrow down the indication for Omalizumab. Therefore, prior to filing the application, the intended patient population was reconsidered. As a result, “patients who have step 3 or step 4 asthma symptoms despite receiving step 4 therapy according to the JGL2003” were considered to be the eligible population for the Omalizumab treatment. To meet these criteria, based on the inclusion criteria for

Study 1304, the eligible population was defined as “patients with asthma symptoms (any of the following conditions is met: daily asthma symptoms; night-time symptoms at least once a week; %FEV_{1.0} < 80% of the predicted value) despite high-dose inhaled corticosteroids [BDP ≥ 800 µg/day or equivalent] plus at least 2 antiasthmatic drugs or oral corticosteroids.” The efficacy and safety of Omalizumab in a subgroup of patients that meets the above-mentioned criteria (target population, 70 of 151 subjects in the Omalizumab group and 91 of 164 subjects in the placebo group) were additionally evaluated.

The primary efficacy endpoint of the mean change in morning PEF from baseline at final assessment was 13.92 L/min in the Omalizumab group and 3.15 L/min in the placebo group and the between-treatment difference and its 95% confidence interval were 10.77 L/min [1.49, 20.04], showing that the mean change was significantly greater in the Omalizumab group than in the placebo group ($P = 0.023$, ANCOVA including treatment group, dosing frequency, and baseline value as covariates) and these results were similar to those from the entire study population.

In the target population, adverse events (including abnormal laboratory changes) occurred in 92.9% of the Omalizumab group (65 of 70 subjects) and 91.2% of the placebo group (83 of 91 subjects). There were no deaths and serious adverse events were reported by 5 subjects (5 events) of the Omalizumab group (enterocolitis, pneumonia NOS, benign mediastinal neoplasm NOS, prostatitis, asthma NOS [one event each]) and 7 subjects (9 events) of the placebo group (asthma NOS [2 events]; pulmonary tuberculosis and bronchial tuberculosis [2 events]; bacterial pneumonia NOS; gastroenteritis NOS; gastric cancer NOS; pain NOS; atrophic gastritis [one event each]) in the target population.

Adverse drug reactions (including abnormal laboratory changes) occurred in 51.4% of the Omalizumab group (36 of 70 subjects) and 45.1% of the placebo group (41 of 91 subjects) and the main events were as shown in the following table.

Table. Main adverse drug reactions in the target population from Study 1304

| Name of event | Omalizumab group N = 70 | Placebo group N = 91 |
|----------------------------|----------------------------|-------------------------|
| Injection site erythema | 18 (25.7) | 6 (6.6) |
| Injection site pruritus | 7 (10.0) | 6 (6.6) |
| Injection site pain | 5 (7.1) | 5 (5.5) |
| Injection site warmth | 5 (7.1) | 5 (5.5) |
| Injection site haemorrhage | 1 (1.4) | 7 (7.7) |
| Injection site swelling | 3 (4.3) | 5 (5.5) |
| Immunology NOS abnormal | 5 (7.1) | 7 (7.7) |

Based on the above, the applicant explained that the clinical response in the target population was similar to that in the overall population and there were also no major differences in the incidence or trend of adverse events between the target and overall populations.

4.(iii).A.(2).3) Long-term treatment study in patients with moderate to severe bronchial asthma (Study 1307) (5.3.5.2-1-1, CIGE025A1307 [November 2003 to March 2006])

An open-label, uncontrolled study in adult patients with moderate persistent to severe persistent bronchial asthma¹¹ inadequately controlled with controllers¹² as recommended by the revised version of the JGL1998 (target number of subjects of ≥ 100) was conducted to evaluate the safety and efficacy of long-term treatment with Omalizumab. The same dosage and dose regimen as for Study 1304 was chosen and the duration of treatment was 48 weeks.

All of the 133 treated subjects were included in the safety analysis and in the FAS for efficacy. Of whom, 124 subjects completed 48-week treatment and 9 subjects were withdrawn from the clinical study: withdrawals due to death (asthma NOS) (1 subject), adverse events (2 subjects) (iron deficiency anaemia and hiatus hernia; urticaria NOS [one case each]), consent withdrawal (1 subject), and other reasons (5 subjects) (2 subjects could not continue the clinical study due to the investigator's death, etc.).

The efficacy endpoint of morning PEF in the FAS was 343.3 ± 114.2 L/min (Mean \pm SD) in the run-in period and 360.6 ± 111.6 L/min in Treatment Weeks 47 to 48.

Adverse events (including laboratory test abnormalities) occurred at an incidence of 98.5% (131 of 133 subjects). One subject died (asthma NOS), but its causal relationship to Omalizumab was denied. Serious adverse events other than this death were reported by 5 subjects (8 events) (asthma NOS; asthma NOS and colonic polyp; iron deficiency anaemia and hiatus hernia; chest pain; metastases to bone and gastritis NOS, one case each), but a causal relationship to Omalizumab was denied for all events and their outcomes were all reported as "resolved or improved" except for metastases to bone.

Adverse drug reactions (including laboratory test abnormalities) occurred at an incidence of 45.9% (61 of 133 subjects) and the main events (events with an incidence of 5% or greater) were injection site erythema (14.3%, 19 of 133 subjects), injection site swelling (9.8%, 13 of 133 subjects), injection site pruritus (6.8%, 9 of 133 subjects), and injection site pain (6.0%, 8 of 133 subjects).

Based on the above, the applicant explained that because there was no trend towards an increase in the incidence of adverse events associated with prolonged duration of treatment and a trend towards improved pulmonary function etc. associated with Omalizumab was maintained until Treatment Week 48, the tolerability and efficacy of Omalizumab up to 48 weeks of treatment were demonstrated.

¹¹ Patients who have been diagnosed with moderate persistent (step 3) or severe persistent (step 4) asthma based on the revised version of the JGL1998 and have a duration of bronchial asthma of at least 1 year

¹² Patients inadequately controlled despite the use of inhaled corticosteroids ($BDP \geq 400$ μ g/day)

4.(iii).A.(3) Japanese clinical studies in patients with seasonal allergic rhinitis

4.(iii).A.(3).1 Placebo-controlled comparative study in patients with seasonal allergic rhinitis (5.3.5.4-2, CIGE0251303 [October 2001 to 2002])

A randomized, double-blind, parallel-group, placebo-controlled, comparative study in patients with moderate to severe Japanese cedar pollen-induced seasonal allergic rhinitis (target number of subjects of 100 [50 subjects per group]) was conducted. The dosage and dose regimen was determined for each patient according to the dosing charts and the duration of treatment was 12 weeks.

All of the 98 treated subjects (48 subjects in the Omalizumab group, 50 subjects in the placebo group) were included in the safety analysis.

Adverse events (including laboratory test abnormalities) occurred in 64.6% of the Omalizumab group (31 of 48 subjects) and 68.0% of the placebo group (34 of 50 subjects). Adverse drug reactions were observed in 39.6% of the Omalizumab group (19 of 48 subjects) and 20.0% of the placebo group (10 of 50 subjects). There were no deaths and one subject in the Omalizumab group had a serious adverse event of ulcerative colitis and its causal relationship to Omalizumab could not be denied. The main adverse drug reactions were injection site erythema (Omalizumab group, 14.6% [7 of 48 subjects]; Placebo group, 4.0% [2 of 50 subjects]), injection site oedema (Omalizumab group, 16.7% [8 of 48 subjects]; Placebo group, 2.0% [1 of 50 subjects]), etc.

4.(iii).A.(3).2 Open-label study in patients with seasonal allergic rhinitis (Readministration study) (5.3.5.4-3, CIGE0251306 [November 2002 to June 2003])

An open-label, uncontrolled study in which Omalizumab was readministered during the Japanese cedar pollen season of the following year to patients who had been treated with Omalizumab in Study 1303 (target number of subjects of 47) was conducted. The dosage and dose regimen was determined in accordance with the dosing charts as in Study 1303 and the duration of treatment was 12 weeks.

All of the 34 treated subjects were included in the safety analysis.

Adverse events (including laboratory test abnormalities) occurred at an incidence of 47.1% (16 of 34 subjects) and adverse drug reactions at an incidence of 14.7% (5 of 34 subjects). There were no deaths or serious adverse events. The main adverse drug reactions were injection site erythema (8.8%, 3 of 34 subjects), injection site pain (5.9%, 2 of 34 subjects), injection site swelling (5.9%, 2 of 34 subjects), etc.

4.(iii).A.(3).3 Suplatast tosilate-controlled comparative study in patients with seasonal allergic rhinitis (5.3.5.4-4, CIGE0251305 [November 2002 to August 2003])

A randomized, double-blind, parallel-group, suplatast tosilate (IPD)-controlled, comparative study in patients with Japanese cedar pollen-induced seasonal allergic rhinitis (target number of subjects of 300 [150 subjects per group]) was conducted. The dosage and dose regimen for Omalizumab was

determined according to the dosing charts and IPD was to be orally administered at a dose of 100 mg 3 times daily after each meal. Subjects were treated with the study drug for 12 weeks using the double dummy method.

All of the 307 treated subjects (154 subjects in the Omalizumab group, 153 subjects in the IPD group) were included in the safety analysis.

Adverse events (including laboratory test abnormalities) occurred in 66.2% of the Omalizumab group (102 of 154 subjects) and 61.4% of the IPD group (94 of 153 subjects) and adverse drug reactions were observed in 29.2% of the Omalizumab group (45 of 154 subjects), and 26.1% of the IPD group (40 of 153 subjects). There were no deaths or serious adverse events. The main adverse drug reactions were injection site erythema (Omalizumab group, 7.8% [12 of 154 subjects]; IPD group, 3.9% [6 of 153 subjects]), injection site haemorrhage (Omalizumab group, 8.4% [13 of 154 subjects]; IPD group, 4.6% [7 of 153 subjects]), injection site pruritus (Omalizumab group, 5.2% [8 of 154 subjects]; IPD group, 0.0% [0 of 153 subjects]), and injection site swelling (Omalizumab group, 8.4% [13 of 154 subjects]; IPD group, 1.3% [2 of 153 subjects]), etc.

4.(iii).A.(4) Foreign clinical studies in patients with bronchial asthma

4.(iii).A.(4).1 Phase II study

(a) Study in moderate to severe patients (5.3.5.1-4, Q0694g [■ 19■ to ■ 19■])

A randomized, double-blind, parallel-group, placebo-controlled, comparative study in adolescent and adult patients with moderate to severe allergic asthma who chronically used oral (≤ 20 mg/day or ≤ 40 mg/2 days of prednisolone or ≤ 16 mg/day of methylprednisolone) or inhaled (≥ 600 μ g/day of triamcinolone) corticosteroids (target number of subjects of 504 [84 subjects each in the low-dose and high-dose placebo groups, 168 subjects each in the low-dose and high-dose Omalizumab groups]) was conducted to evaluate the efficacy and safety of Omalizumab.

On Days 0 and 4, 0.003 mg/kg/[IU/mL] or 0.007 mg/kg/[IU/mL] of Omalizumab or placebo was to be intravenously administered. Then, on Days 7 to 133, 0.006 mg/kg/[IU/mL] or 0.014 mg/kg/[IU/mL] of Omalizumab or placebo was to be intravenously administered every 2 weeks. The duration of treatment was 20 weeks.

All of the 317 treated subjects (105 subjects in the placebo group, 106 subjects in the low-dose Omalizumab group, 106 subjects in the high-dose Omalizumab group) were included in the safety analysis and 306 subjects who continued the study for at least 4 weeks after randomization (100 subjects in the placebo group, 103 subjects in the low-dose Omalizumab group, 103 subjects in the high-dose Omalizumab group) were included in the efficacy analysis.

The primary efficacy endpoint of the change in overall symptom score (daytime and nighttime)¹³ from baseline to 12 weeks (LSMean ± SE) was -0.8 ± 0.12 in the placebo group, -1.3 ± 0.12 in the low-dose Omalizumab group, and -1.3 ± 0.12 in the high-dose Omalizumab group, demonstrating significant reductions in both the high-dose and low-dose Omalizumab groups compared to the placebo group ($P = 0.008$ and $P = 0.005$, respectively; ANOVA).

Adverse events (including abnormal laboratory changes) occurred in 92.4% of the placebo group (97 of 105 subjects), 98.1% of the low-dose Omalizumab group (104 of 106 subjects), and 100% of the high-dose Omalizumab group (106 of 106 subjects). There were no deaths. Serious adverse events were reported by 6 subjects in the placebo group (asthma [3 cases] etc.), 2 subjects in the low-dose Omalizumab group (asthma [2 cases] etc.), and 5 subjects in the high-dose Omalizumab group (asthma [4 cases] etc.), but a causal relationship to Omalizumab was denied for all cases. Adverse events leading to study discontinuation occurred in 5 subjects of the placebo group (dizziness, asthma exacerbation, brain tumor, etc.), 3 subjects of the low-dose Omalizumab group (asthma exacerbation, attack, somnolence), and 3 subjects of the high-dose Omalizumab group (urticaria, anaphylactoid reaction, headache).

Adverse drug reactions were observed in 39.0% of the placebo group (41 of 105 subjects), 38.7% of the low-dose Omalizumab group (41 of 106 subjects), and 35.8% of the high-dose Omalizumab group (38 of 106 subjects) and the main events were as shown in the following table.

Table. Main adverse drug reactions in Study Q694g

| Name of event | Placebo group n = 105 | Low-dose Omalizumab group n = 106 | High-dose Omalizumab group n = 106 |
|-------------------------|--------------------------|---|--|
| Headache | 12 (11.4) | 8 (7.5) | 11 (10.4) |
| Injection site reaction | 4 (3.8) | 8 (7.5) | 6 (5.7) |
| Dizziness | 6 (5.7) | 4 (3.8) | 4 (3.8) |
| Pruritus | 0 (0.0) | 6 (5.7) | 5 (4.7) |
| Urticaria | 3 (2.9) | 4 (3.8) | 7 (6.6) |

4.(iii).A.(4).2) Phase III studies

(a) US study in patients with moderate to severe allergic asthma (Study 008) (5.3.5.1-9, Study 008C [■ 19■ to ■ 19■], Study 008E [through ■ 19■])

A randomized, double-blind, parallel-group, placebo-controlled, comparative study in adolescent and adult patients with moderate to severe persistent allergic asthma inadequately controlled despite daily treatment with inhaled corticosteroids (at doses equivalent to BDP 420-840 µg/day) and as-needed or regular use of short-acting inhaled β₂-agonists (target number of subjects of 550 [225 subjects per group]) was conducted to examine the efficacy and safety of Omalizumab.

The dosage and dose regimen was determined for each patient according to the dosing charts and the

¹³ For patients aged ≥ 17 years, 3 symptoms for morning and 13 symptoms for evening were scored from 1 to 7 and the mean of the 16 scores was calculated.
For patients aged ≤ 16 years, 3 symptoms for morning and 14 symptoms for evening were scored from 1 to 7 and the mean of the 17 scores was calculated.

treatment period was 28 weeks. Inhaled corticosteroid (BDP) was administered at a stable dose for the first 16 weeks of a 28-week treatment period (stable steroid phase) and then in the remaining 12 week-period, the BDP dose was tapered for 8 weeks and the maintenance dose was administered for the last 4 weeks (steroid reduction phase). In order to continue to examine the safety of Omalizumab after this study, a 5-month, double-blind extension study (Study 008E) was conducted.

All of the 525 treated subjects (106 subjects in the Omalizumab every 2 weeks group, 101 subjects in the placebo every 2 weeks group, 162 subjects in the Omalizumab every 4 weeks group, 156 subjects in the placebo every 4 weeks group) were included in the safety and efficacy analyses (ITT: Intention-to-treat).

The primary efficacy endpoint of the number of asthma exacerbations¹⁴ per subject in the ITT population was 0.28 ± 0.95 (0 [0, 7]) (Mean \pm SD (Median [Min, Max])) in the Omalizumab group and 0.54 ± 1.38 (0 [0, 8]) in the placebo group during the stable steroid phase and 0.39 ± 0.92 (0 [0, 5]) in the Omalizumab group and 0.66 ± 1.19 (0 [0, 6]) in the placebo group during the steroid reduction phase and there was a significant difference between the groups during each phase (stable steroid phase, $P = 0.006$; steroid reduction phase, $P = 0.003$, Generalized CMH test adjusted for dosing frequency).

In Study 008C, adverse events (including laboratory test abnormalities) occurred in 89.2% of the Omalizumab group (239 of 268 subjects) and 89.1% of the placebo group (229 of 257 subjects). One death occurred in the placebo group (cardiac arrest) and its causal relationship to the study drug was denied. Other serious adverse events (excluding serious asthma exacerbations) were observed in 7 subjects of the Omalizumab group and 7 subjects of the placebo group. Adverse events leading to treatment discontinuation were noted in 2 subjects of the Omalizumab group and 3 subjects of the placebo group and their causal relationship to the study drug was denied except for 1 case in the placebo group. Injection site reaction occurred in 36.6% of the Omalizumab group (98 of 268 subjects) and 35.4% of the placebo group (91 of 257 subjects).

Adverse drug reactions (including laboratory test abnormalities) were observed in 4.5% of the Omalizumab group (12 of 268 subjects) and 5.1% of the placebo group (13 of 257 subjects) and the main events were headache (3 cases) etc. in the Omalizumab group, and post-injection phenomenon, and pharyngitis (2 cases each), etc. in the placebo group.

¹⁴ An asthma exacerbation was defined as a worsening of asthma requiring treatment with oral or intravenous corticosteroids or a doubling of the inhaled corticosteroid dose from baseline.

(b) Study in patients with moderate to severe allergic asthma conducted mainly in Europe and the US (Study 009) (5.3.5.1-12, Study 009C [■ 19■ to ■ 19■], Study 009E [through ■ 20■])

A randomized, double-blind, parallel-group, placebo-controlled, comparative study in adolescent and adult patients with moderate to severe persistent allergic asthma inadequately controlled despite daily treatment with inhaled corticosteroids (at doses equivalent to BDP 500-1200 µg/day) and as-needed or regular use of short-acting inhaled β₂-agonists (target number of subjects of 550 [225 subjects per group]) was conducted to examine the efficacy and safety of Omalizumab.

The same dosage and dose regimen as for Study 008 was chosen and the treatment period was 28 weeks. Inhaled corticosteroid (BDP) was administered at a stable dose for the first 16 weeks of a 28-week treatment period (stable steroid phase) and then in the remaining 12 week-period, the BDP dose was tapered for 8 weeks and the maintenance dose was administered for the last 4 weeks (steroid reduction phase). In order to continue to examine the safety of Omalizumab after this study, a 5-month, double-blind extension study (Study 009E) was conducted.

All of the 546 treated subjects (127 subjects in the Omalizumab every 2 weeks group, 122 subjects in the placebo every 2 weeks group, 147 subjects in the Omalizumab every 4 weeks group, 150 subjects in the placebo every 4 weeks group) were included in the safety and efficacy analyses (ITT).

The primary efficacy endpoint of the number of asthma exacerbations¹⁵ per subject in the ITT population was 0.28 ± 1.07 (0 [0, 8]) (Mean \pm SD (Median [Min, Max])) in the Omalizumab group and 0.66 ± 1.43 (0 [0, 8]) in the placebo group during the stable steroid phase and 0.36 ± 1.01 (0 [0, 5]) in the Omalizumab group and 0.75 ± 1.42 (0 [0, 6]) in the placebo group during the steroid reduction phase and there was a significant difference between the groups during each phase ($P < 0.001$ for both, Generalized CMH test adjusted for dosing frequency).

In Study 009C, adverse events (including laboratory test abnormalities) occurred in 80.7% of the Omalizumab group (221 of 274 subjects) and 78.3% of the placebo group (213 of 272 subjects). There were no deaths. Serious adverse events excluding serious asthma exacerbations were observed in 9 subjects of the Omalizumab group and 3 subjects of the placebo group, but a causal relationship to the study drug was denied for all cases. Adverse events leading to treatment discontinuation were noted in 0 subject of the Omalizumab group and 5 subjects of the placebo group. Injection site reaction occurred in 49.3% of the Omalizumab group (135 of 274 subjects) and 44.9% of the placebo group (122 of 272 subjects).

Adverse drug reactions occurred in 6.2% of the Omalizumab group (17 of 274 subjects) and 3.7% of the placebo group (10 of 272 subjects) and the main events were fatigue, headache, paraesthesia (3

¹⁵ An asthma exacerbation was defined as a worsening of asthma requiring treatment with oral or intravenous corticosteroids or a doubling of the inhaled corticosteroid dose from baseline.

cases each), moniliasis, rash (2 cases each), etc. in the Omalizumab group and headache (3 cases) etc. in the placebo group.

(c) European study in patients with severe allergic asthma (Study 2306) (5.3.5.1-5, Study 2306 [December 2001 to January 2004]) (Reference data)

A randomized, double-blind, parallel-group, placebo-controlled, comparative study in adolescent and adult patients with severe allergic asthma who had experienced multiple asthma exacerbations or had been hospitalized or attended an emergency room due to a severe asthma exacerbation in the past year despite treatment with high-dose inhaled corticosteroids and a long-acting inhaled β_2 -agonist in accordance with step 4 therapy in the Global Initiative for Asthma (GINA) 2002 guidelines (target number of subjects of 400 [200 subjects per group]) was conducted to determine the efficacy of Omalizumab.

The dosage and dose regimen was determined for each patient according to the dosing charts and the treatment period was 28 weeks.

All of the 482 treated subjects (245 subjects in the Omalizumab group, 237 subjects in the placebo group) were included in the safety analysis and 419 subjects enrolled after the second protocol amendment¹⁶ (209 subjects in the Omalizumab group, 210 subjects in the placebo group) were included in the efficacy analysis (primary ITT).

The primary efficacy endpoint of the rate of asthma exacerbations¹⁷ per study treatment period in the primary ITT population was 0.68 in the Omalizumab group and 0.91 in the placebo group and the between-treatment ratio (Omalizumab group:placebo group) and its 95% confidence interval were 0.738 [0.552, 0.988], demonstrating a significant difference between the groups ($P = 0.042$, Poisson regression analysis including treatment group, dosing frequency, country, antiasthmatic drugs, and baseline value as covariates), when adjusted for baseline asthma exacerbation rate.¹⁸ Unadjusted analysis showed no significant difference.

Adverse events (excluding laboratory test abnormalities) occurred in 72.2% of the Omalizumab group (177 of 245 subjects) and 75.5% of the placebo group (179 of 237 subjects). There were no deaths. Serious adverse events were observed in 29 subjects of the Omalizumab group (47 events) (asthma NOS [24 events], upper respiratory tract inflammation [2 events], cholecystitis [2 events], etc.) and 37 subjects of the placebo group (51 events) (asthma NOS [32 events], pneumonia [2 events], dyspnoea [2 events], etc.), but a causal relationship to the study drug was denied for all events except for asthma

¹⁶ Due to the revision of GINA2002, the doses of inhaled corticosteroids specified in the inclusion criteria were changed from doses equivalent to BDP 800 $\mu\text{g}/\text{day}$ or fluticasone propionate 400 $\mu\text{g}/\text{day}$ to doses equivalent to BDP 1000 $\mu\text{g}/\text{day}$.

¹⁷ An asthma exacerbation was defined as a worsening of asthma requiring treatment with rescue oral or intravenous corticosteroids.

¹⁸ Since more subjects in the Omalizumab group had a history of asthma exacerbation in the 14 months prior to randomization than in the placebo group, adjustment for baseline exacerbations (exacerbations occurring in the 14 months prior to the start of treatment) was performed.

NOS in the Omalizumab and placebo groups (1 event each) and asthma NOS/pruritus/petechiae/papular rash (1 event) in the Omalizumab group. Adverse events leading to treatment discontinuation were reported by 5 subjects of the Omalizumab group (asthma exacerbation [3 cases] etc.) and 3 subjects of the placebo group (asthma exacerbation [1 case] etc.).

Adverse drug reactions (excluding laboratory test abnormalities) occurred in 11.8% of the Omalizumab group (29 of 245 subjects) and 9.3% of the placebo group (22 of 237 subjects) and the main events were nausea, injection site erythema, headache, pruritus (3 cases each), injection site pain, injection site pruritus, injection site reaction, injection site rash, papular rash, urticaria (2 cases each), etc. in the Omalizumab group and headache (7 cases), pruritus (4 cases), muscle cramp (2 cases), excess sweating (2 cases), etc. in the placebo group.

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

4.(iii).B.(1) *Clinical positioning etc. of Omalizumab*

4.(iii).B.(1).1 *Intended patient population for Omalizumab*

It is appropriate to limit the use of Omalizumab to patients who respond inadequately to conventional therapies and in view of the evolution of asthma treatment in recent years, PMDA understands that further narrowing down the intended patient population from the study population for Study 1304 is unavoidable. PMDA asked the applicant to provide more detailed explanation about the appropriateness of the definition of “the target population” in Study 1304, taking account of the consistency with the JGL criteria etc.

The applicant explained as follows:

Referring to the JGL2003 that had been published at the time of filing the application, we considered that the appropriate definition of “the target population,” i.e. patients who respond inadequately to conventional therapies, was “patients who have step 3 (corresponding to moderate persistent) or step 4 (corresponding to severe persistent) asthma symptoms despite receiving step 4 therapy, which is the best available therapy as defined by the JGL2003.” In accordance with the JGL, “Step 4 therapy” was defined as (a) inhaled corticosteroids at doses equivalent to BDP \geq 800 μ g/day plus (b) at least 2 other controllers or continuous use of oral corticosteroids. “Step 3 or step 4 asthma symptoms” was defined as follows, taking into account that the JGL [see the table below] states that “if one of the features (symptom and lung function) of severity is present, the applicable step should be considered.” Among 5 inclusion criteria as to symptoms and lung function for Study 1304 (nighttime awakenings due to asthma symptoms \geq 1 day/week; activities of daily living are limited by asthma symptoms; symptoms requiring rescue medication [short-acting inhaled β_2 -agonists] \geq 1 day/week; PEF diurnal variability \geq 20% \geq 1 day/week; mean FEV_{1.0} or PEF during the run-in period is 40%-80% of the normal predicted value), the following 3 symptoms meeting the step 3 criteria were selected as the conditions for the target population: (a) daily asthma symptoms, (b) nighttime symptoms once a week, and (c) %FEV_{1.0} is $<$ 80% of the predicted value. Patients meeting any of these 3 conditions were considered to have step 3 or step 4 asthma symptoms. Although the defined clinical features of the

target population do not meet all of the JGL2003 criteria, as the necessity of treatment with Omalizumab is determined comprehensively based on not only clinical features but also the treatment level, there should be no major differences in identifying patients who respond inadequately to conventional therapies as compared to assessment based on the JGL.

Table. JGL2003 severity classification and stepwise approach to drug therapy (Step 3 and Step 4)

| Severity | Step 3 Moderate Persistent | Step 4 Severe Persistent |
|---|--|--|
| Symptom features | <ul style="list-style-type: none"> • Daily symptoms • Almost daily use of short-acting inhaled β_2-agonist • Activities of daily living and sleep are affected ≥ 1 time a week • Nighttime symptoms ≥ 1 time a week | <ul style="list-style-type: none"> • Frequent exacerbations even with treatment • Daily symptoms • Limited activities of daily living • Frequent nighttime symptoms |
| PEF | 60%-80% of the predicted value | < 60% of the predicted value |
| FEV _{1.0} | 60%-80% of the predicted value, variability $\geq 30\%$, or PEF is 60%-80% of the personal best value | variability $\geq 30\%$, or PEF < 60% of the personal best value |
| Controllers ● Continuous use ○ Consider | <ul style="list-style-type: none"> ● Continuous use of inhaled corticosteroids (mid-dose^{a)}) Use one or more of the following drugs with inhaled corticosteroids. <ul style="list-style-type: none"> • Theophylline sustained-release preparation • Long-acting β_2-agonist (inhaled/patch/oral) • Leukotriene antagonist ○ Consider concomitant use of Th2 cytokine inhibitor | <ul style="list-style-type: none"> ● Continuous use of inhaled corticosteroids (high-dose^{a)}) Use two or more of the following drugs with inhaled corticosteroids. <ul style="list-style-type: none"> • Theophylline sustained-release preparation • Long-acting β_2-agonist (inhaled/patch/oral) ○ Consider concomitant use of Th2 cytokine inhibitor ● If poorly controlled by the above <ul style="list-style-type: none"> • Add oral corticosteroids |
| For attacks | Short-acting inhaled β_2 -agonist | Short-acting inhaled β_2 -agonist |

a) Mid-dose: 400 to 800 μg in BDP equivalents, High-dose: 800 to 1600 μg in BDP equivalents

Furthermore, the JGL2006 has now been published and there are no major differences between the JGL2006 and JGL2003, except that “classification of asthma severity taking account of ongoing therapy” has been specified and oral corticosteroids are handled differently (“If poorly controlled by the above, add oral corticosteroids” in the above table has been changed to “If poorly controlled by all of the above” in the JGL2006). Thus, also in light of the JGL2006, the definition of “the target population” should be appropriate.

PMDA concluded that it is possible to evaluate the efficacy and safety of Omalizumab in a newly defined population based on the results from Study 1304 since the definition of “the target population” seems appropriate in light of the current asthma treatment and there have been no major differences in the results between the overall and target populations in Study 1304.

Also, because it is important to carefully determine the risks and benefits of Omalizumab prior to its use and ensure compliance with its proper use, PMDA considers that it is necessary to clearly specify the intended population for Omalizumab in the INDICATION and PRECAUTIONS sections of the package insert and furthermore, the use of Omalizumab should be limited to physicians etc. who are familiar with treatment of severe asthma so as to ensure correct diagnosis and selection of eligible patients and compliance with its proper use.

4.(iii).B.(1).2) Choice between Omalizumab and oral corticosteroids

The JGL recommends the use of oral corticosteroids if symptoms are poorly controlled by other treatments and the positioning of oral corticosteroids is similar to the anticipated positioning of Omalizumab. Thus, PMDA asked the applicant to explain their view on the choice between Omalizumab and oral corticosteroids.

The applicant explained as follows:

The use of oral corticosteroids as a controller is limited because there is a concern about systemic adverse drug reactions etc. and oral corticosteroids should rather be considered as a reliever. Therefore, oral corticosteroids are positioned differently from Omalizumab and regardless of the use of oral corticosteroids, Omalizumab can be used.

Although oral corticosteroids are mainly used as a reliever, there are some patients with severe asthma requiring oral corticosteroids for long-term management of the disease. Therefore, PMDA considers that adequate information on the safety and efficacy of Omalizumab should be collected with cooperation of relevant academic societies etc., to determine the eligible patient populations for oral corticosteroids and Omalizumab, the choice between oral corticosteroids and Omalizumab, etc.

4.(iii).B.(2) Efficacy

PMDA asked the applicant to provide a justification for choosing “morning PEF” as the primary endpoint for Japanese Study 1304, taking account of the background of choosing “the frequency of asthma exacerbations” as the primary endpoint for foreign confirmatory studies.

The applicant explained as follows:

In the US, as a result of a discussion with the US Food and Drug Administration (FDA), it was concluded that as Omalizumab is a biopharmaceutical product, a clinically significant outcome measure should be used for efficacy evaluation and asthma exacerbations (the definitions of an asthma exacerbation included a worsening of asthma requiring treatment with rescue systemic corticosteroids in clinical studies of Omalizumab), which are the biggest concern for severe asthma patients at high risk of asthma death, are most appropriate as the primary endpoint. In Europe, in accordance with the statement of the Committee for Proprietary Medicinal Products (CPMP)’s guideline, “Note for guidance on the clinical investigation of medicinal products in the treatment of asthma” (2002): “The selection of the most appropriate primary endpoint will depend on the grade of asthma severity and symptom-based endpoints are particularly important for moderate and severe persistent asthma. These may include the frequency of exacerbations and an assessment of asthma control,” the rate of asthma exacerbations was selected as the primary endpoint for Study 2306. On the other hand, also for Japanese Study 1304, selecting the rate of asthma exacerbations as the primary endpoint was considered, but given up because the number of subjects required was estimated to be about ■■■ to ■■■ and it seemed very difficult to conduct the study in Japan alone. Then, referring to “FY 1998 Report on Guideline for the Development of Antiallergic Drugs prepared by the Research Group for

Draft Development as the MHW-sponsored project” etc., PEF, which is an objective and standard measure for evaluation of antiasthmatic drugs and is widely used for daily management of asthma patients’ conditions, was chosen as the primary endpoint. In addition to PEF assessment, the use of rescue medication and the symptom scores etc. were selected as secondary endpoints and furthermore, though an exploratory endpoint, asthma exacerbations were also assessed. By evaluating these endpoints together, the effects on overall asthma control can be assessed. Therefore, we consider that the efficacy evaluation method in this study was appropriate.

PMDA asked the applicant to explain in detail about their view on whether it can be concluded that the clinically significant efficacy of Omalizumab has been demonstrated, taking into account that the between-treatment difference in the change in morning PEF in Study 1304 (13.19 L/min in the overall population, 10.77 L/min in the target population) was numerically small.

The applicant explained as follows:

With respect to PEF improvement, the categories of “marked improvement (improvement of ≥ 40 L/min),” “moderate improvement (improvement of ≥ 20 L/min),” “slight improvement (improvement of ≥ 10 L/min),” “no change (change < 10 L/min),” and “worsening (worsening of ≥ 10 L/min)” have been used as outcome measures (Miyamoto et al., *Journal of Clinical Therapeutics and Medicine*. 2001;17:519-558). Miyamoto et al. have also examined the relationship between global improvement assessment that has conventionally been used in clinical studies and PEF values and have reported that the above categories agreed well with changes in global improvement and an improvement in PEF of ≥ 10 L/min corresponds to “slight improvement” or better in global improvement assessment, although the severity of patients assessed is unknown (Miyamoto et al., *Japanese Journal of Allergology*. 1999;48:576-588). Improved lung function observed after treatment with Omalizumab is considered to result from overall improvement of the disease condition due to the interruption of the allergic inflammatory cascade initiated upon antigen exposure. It is unlikely that Omalizumab which has no direct bronchodilator effect causes a major improvement in PEF. Furthermore, in the patients included in Study 1304, in addition to high-dose inhaled corticosteroids, at least one of a long-acting inhaled β_2 -agonist, a theophylline sustained-release preparation, and a leukotriene antagonist had already been used, which probably left little room for improvement in PEF. Taking account of these factors, an improvement in PEF of ≥ 10 L/min, which corresponds to “slight improvement” or better in global improvement assessment as reported by Miyamoto et. al, observed in this patient population, can be interpreted as a sufficiently significant change.

PMDA asked the applicant to explain the reason for no significant improvements in the symptom scores (symptom score, activities of daily living score, nighttime sleep score) and the use of rescue medication in Study 1304.

The applicant explained as follows:

The sample size for Study 1304 was determined based on morning PEF and the study was not

designed to detect a significant difference in the symptom scores or the use of rescue medication. Also, patients were included in the study when they met any of the 5 criteria for identifying patients with inadequately controlled asthma (nighttime awakenings due to asthma symptoms ≥ 1 day/week); activities of daily living are restricted by asthma symptoms; symptoms requiring rescue medication (short-acting inhaled β_2 -agonists) ≥ 1 day/week); PEF diurnal variability $\geq 20\%$ (≥ 1 day/week); the mean FEV_{1.0} or PEF during the run-in period is 40% to 80% of the normal predicted value). As a result, there were some subjects who did not use rescue medication at baseline and those with a symptom score, an activities of daily living score, or a nighttime sleep score of 0 at baseline. Due to the influences of these subjects, the baseline value of each variable was relative low, resulting in no significant improvement. When analysis was performed with patients who used rescue medication at baseline or those who had a symptom score, an activities of daily living score, or a nighttime sleep score greater than 0 at baseline, the between-treatment difference was larger for all variables compared to the FAS, as shown in the following table. Also, when a similar analysis was performed for the target population, there was a similar trend.

Table. Use of rescue medication, symptom score, activities of daily living score, and nighttime sleep score at final assessment (at Week 16) in Study 1304

| | | Overall population (FAS) | | Population with score greater than 0 at baseline | |
|-----------------------------------|------------------------------------|------------------------------|---------------------|--|-----------------------|
| | | Omalizumab group | Placebo group | Omalizumab group | Placebo group |
| Use of rescue medication per week | N | 151 | 164 | 90 | 106 |
| | Baseline value | 8.0 \pm 14.3 | 7.4 \pm 13.7 | 13.4 \pm 16.4 | 11.5 \pm 15.6 |
| | Mean change ^{a)} [95% CI] | -1.43 [-2.67, -0.19] | -0.38 [-1.57, 0.82] | -2.61 [-4.64, -0.58] | -0.95 [-2.83, 0.93] |
| | Difference [95% CI] P-value | -1.05 [-2.77, 0.67] 0.229 | | -1.66 [-4.41, 1.10] 0.238 | |
| Symptom score | N | 151 | 164 | 117 | 142 |
| | Baseline value | 7.9 \pm 8.9 | 9.7 \pm 11.5 | 10.2 \pm 8.9 | 11.2 \pm 11.6 |
| | Mean change ^{a)} [95% CI] | -2.14 [-3.50, -0.79] | -0.41 [-1.72, 0.90] | -2.89 [-4.58, -1.20] | -0.64 [-2.18, 0.90] |
| | Difference [95% CI] P-value | -1.73 [-3.62, 0.15] 0.072 | | -2.25 [-4.53, 0.04] 0.054 | |
| Activities of daily living score | N | 151 | 164 | 73 | 94 |
| | Baseline value | 20.0 \pm 29.0 | 20.4 \pm 27.4 | 41.3 \pm 29.4 | 35.5 \pm 27.7 |
| | Mean change ^{a)} [95% CI] | -2.82 [-5.97, 0.33] | -1.92 [-4.97, 1.12] | -9.44 [-15.16, -3.72] | -6.52 [-11.60, -1.43] |
| | Difference [95% CI] P-value | -0.90 [-5.27, 3.47] 0.687 | | -2.93 [-10.59, 4.74] 0.452 | |
| Nighttime sleep score | N | 151 | 164 | 77 | 100 |
| | Baseline value | 10.2 \pm 14.5 | 10.4 \pm 13.0 | 20.1 \pm 14.6 | 17.1 \pm 12.7 |
| | Mean change ^{a)} [95% CI] | -2.13 [-3.77, -0.49] | -1.39 [-2.98, 0.19] | -5.59 [-8.43, -2.75] | -3.75 [-6.26, -1.23] |
| | Difference [95% CI] P-value | -0.74 [-3.01, 1.54] 0.524 | | -1.85 [-5.64, 1.95] 0.338 | |

a) LSMean calculated from an ANCOVA model including treatment group, dosing frequency, and baseline value as covariates

Moreover, PMDA asked the applicant to identify patients who meet the definition of the target population in Foreign Study 2306, which was conducted under relatively similar conditions as Japanese Study 1304, and to evaluate the change in morning PEF in this population compared to the target population of Study 1304.

The applicant explained as follows:

For the target population of Foreign Study 2306 (Note that because it was stated in the inclusion criteria that Study 2306 had to include patients who had experienced multiple asthma exacerbations in the past year, etc., the severity of the disease in this population is considered to be slightly higher than

in the target population of Study 1304), the data were summarized in the same manner as for Study 1304, i.e. based on the summarized data from baseline to Week 16 (the onset of asthma exacerbation if asthma exacerbation occurs before Week 16), the change in morning PEF was calculated. As a result, as shown in the following table, similar results as those from the target population of Study 1304 were obtained. Although the annual asthma exacerbation rate in the target population of Study 2306 (adjusted for baseline value) was 1.542 in the Omalizumab group and 2.084 in the placebo group and the between-treatment ratio and its 95% confidence interval were 0.740 [0.523, 1.046], showing no significant difference between the groups ($P = 0.088$, Poisson regression analysis including treatment group, dosing frequency, country, antiasthmatic drugs, and baseline value as covariates), these results were similar to those from the overall population of Study 2306.

Table. Change in morning PEF in the target population of Study 2306

| Patient population | Omalizumab group Estimated value* | Placebo group Estimated value* | Difference (L/min) * [95% CI] | P-value |
|--|--------------------------------------|-----------------------------------|----------------------------------|---------|
| Study 1304 (Omalizumab group n = 70, Placebo group n = 91) | 13.92 | 3.15 | 10.77 [1.49, 20.04] | 0.0232 |
| Study 2306 (Data were summarized in the same manner as for Study 1304) (Omalizumab group n = 100, Placebo group n = 98) | 19.89 | 5.77 | 14.12 [1.75, 26.48] | 0.025 |

*: ANCOVA model including treatment group, dosing frequency, and baseline PEF as covariates for Study 1304

ANCOVA model including treatment group, dosing frequency, baseline PEF, gender, country, and antiasthmatic drugs as covariates for Study 2306

PMDA considers as follows:

Taking into account that the intended population for Omalizumab is severe asthma patients, the most appropriate efficacy endpoint is “the rate of asthma exacerbations” used in foreign studies, but it is understandable that the applicant considered it difficult to choose “the rate of asthma exacerbations” in terms of the feasibility of the study in Japan and does not deny the use of “morning PEF” as an alternative outcome measure. Although the difference in the change in morning PEF between the Omalizumab and placebo groups in the target population of Study 1304 was around 10 L/min, which was numerically small, a trend towards improvement of symptoms etc. was also suggested. It should also be taken into consideration that there is little room for improvement in lung function due to the influence of airway remodelling in patients with difficult-to-control severe asthma. Also in Foreign Study 2306 demonstrating the reduction of asthma exacerbations, similar outcomes were observed regarding the change in PEF. In light of these findings, Omalizumab’s contribution to asthma control is appreciable to a certain extent.

On the other hand, the applicant explained that an exploratory assessment of the effect on asthma exacerbations was performed also in Study 1304, which suggested the inhibitory effects of Omalizumab. However, PMDA considers that sufficient data for evaluation have not been presented, for example, no information on asthma exacerbation experience before the start of the study is available. Considering that Omalizumab is a biopharmaceutical product with a new mode of action and the safety of long-term treatment with Omalizumab etc. has not fully been established, its contribution to reduction of asthma exacerbations (reduction of the risk of asthma death) should be further investigated via post-marketing surveillance also in Japan in order to further define the clinical

significance of Omalizumab.

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

4.(iii).B.(3).1 Justification for dose determination method

PMDA asked the applicant to provide a justification for determining doses of Omalizumab based on baseline serum total IgE level, instead of specific IgE level, taking account of the influences of the ratio of specific IgE level to total IgE level in serum on the efficacy of Omalizumab, etc.

The applicant explained as follows:

Using blood samples that were collected before the start of treatment from subjects of Foreign Study 2306 and were stored frozen (among the 410 subjects, 337 subjects whose samples were analyzed again were assessed), levels of antigen-specific IgE to 8 different allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, German cockroach, oriental cockroach, *Aspergillus fumigatus*, *Alternaria alternate*) in individual patients were quantitated and the relationship between total IgE level and the sum of different specific IgE levels was investigated post-hoc. As a result, there was a trend towards an increase in the sum of different specific IgE levels with increasing total IgE level, while there was no clear relationship between total IgE level and the ratio of the sum of different specific IgE levels to total IgE level. Because foreign clinical studies indicated that the efficacy of Omalizumab tended to be low in patients with low baseline total IgE levels, assuming that the ratio of specific IgE level to total IgE level may affect the efficacy of Omalizumab in patients with low total IgE levels, the asthma exacerbation rate was compared among the quartile categories of specific IgE levels (highest quartile, upper-middle quartile, lower-middle quartile, lowest quartile, 30 subjects per quartile) in a group of patients with low total IgE levels (≤ 100 IU/mL) in Study 2306. As a result, the effect of Omalizumab in reducing asthma exacerbations was highest in the lower-middle quartile and lowest in the highest quartile, but the number of subjects was limited and no clear trend was observed. Also when the efficacy was compared among the quartile categories of specific IgE levels for other endpoints, there was no consistent trend. Therefore, the necessity of determining doses focusing on specific IgE levels has not been suggested. Furthermore, asthma patients are often tested positive for multiple inhaled antigens, in which case it is generally difficult to identify all causative antigens, and unknown IgE-mediated antigens may exist. Thus, dose determination based on total IgE level should be a reasonable and appropriate method.

The recommended clinical dose of Omalizumab has been chosen as a dose that can maintain serum free IgE levels below 25 ng/mL, based on the relationship between clinical benefit and serum free IgE level in foreign clinical studies. PMDA asked the applicant to demonstrate the relationship between morning PEF (the primary endpoint for the Japanese study) and serum free IgE levels and then provide a justification for selecting a similar dosage and dose regimen to that in foreign countries for the use in Japan.

The applicant explained that when the data from Japanese Study 1304 were stratified by serum free

IgE level at final assessment (Week 16) and the relationship between serum free IgE levels and changes in morning PEF was investigated, as shown in the following table, statistically significant PEF improvement was seen in the group of subjects with serum free IgE levels ≤ 25 ng/mL as compared to the group of subjects with serum free IgE levels > 150 ng/mL, and there should be no problem with using a similar dosage and dose regimen to that in foreign countries in Japan.

Table. Serum free IgE levels and morning PEF in Study 1304

| Group | Free IgE level (ng/mL) | n | No. of cases in the Omalizumab group | Change from baseline ^{a)} (L/min) | Difference vs. Group 4 | P-value ^{b)} |
|-------|------------------------|-----|--------------------------------------|--|------------------------|-----------------------|
| 1 | ≤ 25 | 134 | 133 | 16.26 | 12.45 | 0.0019 |
| 2 | $25 < -50$ | 12 | 8 | 2.48 | -1.33 | 0.8911 |
| 3 | $50 < -150$ | 19 | 1 | -0.37 | -4.18 | 0.6024 |
| 4 | $150 <$ | 128 | - | 3.81 | - | - |

a) Least-square mean, b) ANCOVA

Taking into account that there is a group of patients who are assigned doses that diverge considerably from the optimal dose (0.016 mg/kg/[IU/mL]/4 weeks, 0.008 mg/kg/[IU/mL]/2 weeks) when using the dosing charts, PMDA asked the applicant to explain the appropriateness of the dosing charts from a safety point of view.

The applicant explained as follows:

According to the dosing charts used in clinical studies, the dose for a patient with a body weight of 30 kg and an IgE level of 30 IU/mL is 0.167 mg/kg/[IU/mL]/4 weeks, i.e. the highest dose in the charts, indicating that there is a maximum of about a 10-fold difference from the optimal dose. However, when patients from Japanese Study 1304 were stratified into doses ≥ 2 -fold the optimal dose and doses < 2 -fold the optimal dose and the incidence of adverse events reported in the Omalizumab group (Incidence of overall adverse events, 90.5% [38 of 42 subjects] and 89.9% [98 of 109 subjects], respectively) etc. was compared, there were no major differences between the dose groups. Thus, there should be no particular problem with using the dosing charts.

The current Company Core Data Sheet (CCDS) contains dosing charts modified from those used in clinical studies, where the body weight categories of ≤ 60 kg and > 90 kg are subdivided (Table below). By using these dosing charts instead of the previous ones, it is possible to reduce a gap between the assigned dose and the optimal dose. Therefore, also in Japan, the CCDS's dosing charts (Note that because Omalizumab is indicated for adult patients in Japan, the cells corresponding to body weight ≤ 30 kg will be deleted) will be used after the market launch and the DOSAGE AND ADMINISTRATION section (draft) will accordingly be modified as follows.

[Dosage and administration]

The usual adult dosage is 75 to 375 mg of Omalizumab (Genetical Recombination) administered by subcutaneous injection every 2 or 4 weeks. Doses and dosing frequency are determined by serum total IgE level, measured before the start of treatment, and body weight (the underlined part represents the

change).

Table. Dosing charts presented in the current Omalizumab CCDS

| Administration Every 4 Weeks | | | | | | | | | | | |
|-------------------------------|------------------|---------|---------|---------|---------|---------|---------|---------|------------------------------|-----------|--|
| Serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | | | |
| | > 20-25 | > 25-30 | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| ≥ 30-100 | 75 mg | 75 mg | 75 mg | 150 mg | 150 mg | 150 mg | 150 mg | 150 mg | 300 mg | 300 mg | |
| > 100-200 | 150 mg | 150 mg | 150 mg | 300 mg | Administration every 2 weeks | | |
| > 200-300 | 150 mg | 150 mg | 225 mg | 300 mg | 300 mg | | | | | | |
| > 300-400 | 225 mg | 225 mg | 300 mg | | | | | | | | |
| > 400-500 | 225 mg | 300 mg | | | | | | | | | |
| > 500-600 | 300 mg | 300 mg | | | | | | | | | |
| > 600-700 | 300 mg | | | | | | | | | | |

| Administration Every 2 Weeks | | | | | | | | | | | |
|-------------------------------|------------------|---------|---------|---------|---------|---------|---------|------------------------------|-------------------|-----------|--------|
| Serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | | | |
| | > 20-25 | > 25-30 | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| 30-100 | | | | | | | | | | | |
| > 100-200 | | | | | | | | Administration every 4 weeks | | 225 mg | 300 mg |
| > 200-300 | | | | | | 225 mg | 225 mg | 225 mg | 300 mg | 375 mg | |
| > 300-400 | | | | 225 mg | 225 mg | 225 mg | 300 mg | 300 mg | Do not administer | | |
| > 400-500 | | | 225 mg | 225 mg | 300 mg | 300 mg | 375 mg | 375 mg | | | |
| > 500-600 | | 225 mg | 300 mg | 300 mg | 375 mg | | | | | | |
| > 600-700 | 225 mg | 225 mg | 300 mg | 375 mg | | | | | | | |

PMDA considers as follows:

At present, there are no major problems with Omalizumab dose determination based on baseline serum total IgE level. Theoretically, however, the efficacy of Omalizumab is achieved through a reduction in specific IgE levels. Thus, it is necessary to fully investigate the relationship between specific IgE levels and the efficacy of Omalizumab and further confirm the appropriateness of the dose determination method.

There are no particular problems with the use of the CCDS's dosing charts, but even when the dosing charts are used, determining doses of Omalizumab is complicated. Therefore, in order to ensure the prevention of medication errors, it is necessary to inform how to use the dosing charts (how to use the charts) and provide adequate information, including the dosing rationale, to the medical practice.

4.(iii).B.(3).2) Method of responder assessment etc.

PMDA asked the applicant to explain how to assess treatment response to Omalizumab and the appropriate timing of assessment in clinical practice.

The applicant explained as follows:

For Foreign Study 2306, response or non-response was evaluated based on each of efficacy outcome measures of daytime symptoms, nighttime symptoms, nighttime awakenings, lung function, QOL, and

the physician's Global Evaluation of Treatment Effectiveness (GETE)¹⁹ and the proportion of responders and the asthma exacerbation rates in the responder and non-responder groups were compared among the outcome measures to identify an outcome measure highly correlated with reduction of asthma exacerbations. As a result, when response was evaluated using the GETE (a responder was defined as a rating of "excellent" or "good"), the proportion of responders was as high as 60.5% and the asthma exacerbation rates in the responder and non-responder groups were 0.6 and 2.6, respectively, and the severe asthma exacerbation rates were 0.2 and 1.4, respectively, demonstrating lower rates in the responder group. These results suggested that the GETE was highly correlated with reduction of asthma exacerbations, compared to other outcome measures. Furthermore, the overlap of patients judged as responders among the different outcome measures was analyzed. As a result, patients judged as responders by the GETE overlapped with a majority of patients judged as responders by individual outcome measures and especially, there was a high level of agreement (79.6%) with patient's self-assessment of QOL. Taking account of these findings, the GETE (or an equivalent global outcome measure) is considered to be a useful measure for identifying responders to Omalizumab. Although assessment by the GETE was not performed in Japanese clinical studies, the information on global assessment by the GETE as well as assessment by individual outcome measures such as lung function will be collected through post-marketing surveillance etc. in order to determine whether the GETE is a practicable method in Japan.

The applicant also explained as follows:

The number of FcεR1s on mast cells, basophils, dendritic cells, etc. needs to be minimized in order to maximize the inhibitory effect of Omalizumab on allergic reactions, but it will take several weeks to several months. The results from Japanese and foreign clinical studies have also shown that the efficacy of Omalizumab peaks at 12 to 16 weeks after the start of treatment and is maintained thereafter. Taking account of these findings, it is recommended that treatment response to Omalizumab should be assessed at at least 12 to 16 weeks after the start of treatment.

PMDA asked the applicant to explain the appropriateness of reducing the dose of Omalizumab in patients with improved asthma control after administration of Omalizumab.

The applicant explained as follows:

Although dose reduction following improvement of asthma control after administration of Omalizumab has not been investigated in Japanese and foreign clinical studies, Foreign Study Q0673g has shown that serum free IgE levels gradually return to the baseline levels within 1 year after the discontinuation of Omalizumab. In Foreign Study 2306, asthma symptoms, lung function, the use of rescue medication, etc. worsened with decreasing blood Omalizumab levels after the discontinuation of treatment. Taking account of these findings, the dose of Omalizumab should not be reduced even in

¹⁹ GETE is a measure of asthma control established by Novartis Pharma and is rated on a 5-point scale: "excellent," "good," "moderate," "poor," and "worsening," based on patient interview, patient diary (if used), lung function tests, asthma exacerbations, and unscheduled medical visits, taking account of patient's pre-treatment severity of asthma, level of asthma control, and symptoms.

patients with improved asthma control after the administration of Omalizumab and the dosage and dose regimen determined at the start of treatment needs to be continued.

PMDA considers as follows:

Assessment of treatment response to Omalizumab using a global outcome measure, e.g. the GETE, may be referred to in clinical practice and information on such a outcome measure should be provided so as to ensure that unnecessary prolonged administration of Omalizumab is avoided. However, the GETE has been examined as a method that can judge the effect of Omalizumab in reducing asthma exacerbations, based on foreign clinical study data. In future, therefore, taking also account of the effect of Omalizumab in reducing asthma exacerbations in Japan, its usefulness should be further investigated. To determine the necessity of maintaining the dosage and dose regimen in patients with improved asthma control, it is essential to collect information on the cases of discontinuation/interruption of Omalizumab etc. and then further investigate the impact of dose reduction and interruption/discontinuation of Omalizumab on its efficacy and safety, thereby providing such information to the medical professionals.

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

4.(iii).B.(4).1 Anaphylaxis

PMDA asked the applicant to explain whether an adequate caution statement about anaphylaxis is included in the Japanese package insert (draft), taking account of the background of strengthening the label warning about anaphylaxis in 2007 in the US and Europe and an update on the occurrence of anaphylaxis in the overseas marketing experience.

The applicant explained as follows:

As of December 2006, the incidence of anaphylaxis/anaphylactoid reaction (anaphylaxis) in Japanese and foreign clinical studies up to phase III was 0.13% (7 of 5367 subjects) in the Omalizumab group and 0.03% (1 of 3087 subjects) in the placebo group. Meanwhile, when the occurrence of anaphylaxis was investigated using Sampson's definition (Sampson HA et al., *J Allergy Clin Immunol.* 2005;115:584-91, Sampson HA et al., *J Allergy Clin Immunol.* 2006;117:391-7) based on the overseas post-marketing spontaneous report database from June 2003 to December 2006, 124 patients were identified as anaphylaxis cases and its estimated incidence was about 0.2% (calculated based on the estimated number of patients prescribed Omalizumab of 57300), which was slightly higher than the incidence in clinical studies. Analysis of these 124 cases suggested a generally known trend of occurrence of anaphylaxis (e.g. the incidence is higher among women, patients with anaphylaxis often have some type of allergy, anaphylaxis occurs early after the start of administration in many cases). In addition, as a feature of anaphylaxis associated with Omalizumab, delayed reactions tended to occur (e.g. not a small proportion of the patients [$\geq 30\%$] developed anaphylaxis beyond 2 hours after administration, there were cases where the signs and symptoms persisted for as long as over 1 hour and progressed). Therefore, in the US in June 2007, a Boxed Warning etc. were added to the package insert, which include the following statements: "delayed anaphylaxis has been reported to occur after

administration of Omalizumab” and “patients should be closely observed for an appropriate period of time after Omalizumab administration.” Also, based on similar safety information, in May 2007, the information on delayed anaphylaxis was added to the European labeling to strengthen the warning. According to the latest information from January 2007 to December 2007, there were 70 cases of anaphylaxis (Sampson’s definition was not used) (61 cases from post-marketing spontaneous reporting, 9 cases from post-marketing clinical studies) reported from post-marketing spontaneous reporting (the estimated number of patients exposed, 20000 person-year [January to June 2007], 18500 person-year [July to December 2007]) and clinical studies (including post-marketing clinical studies) (9000 cases [January to June 2007], 7200 cases [July to December 2007]) and the estimated incidence based on post-marketing spontaneous reporting was 0.16% and there have been no major changes in the trend of occurrence, including the development of delayed reactions (of the 51 cases with known time of onset, anaphylaxis occurred beyond 2 hours after administration in 16 cases). Although anaphylaxis has not been reported in Japanese clinical studies, in view of the above situation, as in foreign countries, the Japanese package insert will also include adequate caution statements in the Important Precautions and Clinically significant adverse reactions sections, such as “anaphylaxis including delayed reactions may occur” and “patients should be fully informed of the symptoms of anaphylaxis.”

PMDA asked the applicant to explain the mechanism of the development of anaphylaxis associated with Omalizumab.

The applicant explained as follows:

Although the details are unknown, Omalizumab molecule contains $\leq 5\%$ murine residues, which is expected to minimize the potential for inducing an immune response. However, in some patients, the amino acid sequence may be recognized as a foreign body, leading to immunization and induction of anti-Omalizumab reaction. In such a case, an IgG reaction generally occurs, but an IgE reaction may occur in patients with atopic disease and it has been reported that the incidence of anaphylaxis is generally high, especially in patients with severe allergic asthma (González-Pérez A et al., *European Respiratory Journal*. 2007;30[suppl 30]). On the other hand, in patients who developed immediate hypersensitivity after the first dose, IgE antibody with crossreactivity with Omalizumab that was pre-existing in the body or IgE antibody against polysorbate 20 as a stabilizer used in Omalizumab, may have been involved and anaphylactoid reaction may occur. No anti-Omalizumab antibodies have been detected in anaphylaxis cases though only 2 patients were tested.

PMDA considers that caution statements about anaphylaxis in the proposed package insert are appropriate at present, but it is important to fully investigate the occurrence of anaphylaxis in Japan, antibody formation in patients with anaphylaxis, risk factors, etc. through post-marketing surveillance and provide the obtained information to healthcare professionals and patients promptly. It is also necessary to further investigate its mechanism of development to help formulate more appropriate safety measures.

4.(iii).B.(4).2 Malignant neoplasms

PMDA asked the applicant to explain the reason for differences in the results of assessment of the relationship of malignancies to Omalizumab between the US and European labelings and to provide the applicant's view on the risk of malignancies associated with Omalizumab, based on the latest information on the occurrence of malignancies.

The applicant explained as follows:

In the FDA's review, the assessment of the relationship between malignancies and Omalizumab was performed based on the results from clinical studies completed by September 2002. Since there was an imbalance in the incidence of malignancies between the Omalizumab group (0.5% [20 of 4127 subjects]) and the control group (0.2% [5 of 2236 subjects]), it was stated in the labeling that "the impact of longer exposure to Xolair or use in patients at higher risk for malignancy is not known." Furthermore, the conduct of a 5-year, prospective cohort study whose primary objective was to investigate the risk of malignancies associated with long-term use in patients with moderate to severe allergic asthma (Study Q2948 [EXCELS]) was requested. On the other hand, the incidence of malignancies in clinical studies at the time of regulatory submission in Europe was 0.5% (25 of 5015 subjects) in the Omalizumab group and 0.18% (5 of 2854 subjects) in the control group, which were not substantially different from those at the time of filing in the US, but as new information, the standardized incidence ratio (the ratio of the observed-to-expected number of subjects based on SEER) was calculated based on the US epidemiologic data (Surveillance epidemiology and end result program, SEER). The standardized incidence ratio in the Omalizumab group at the time of US submission was 1.7 (95% CI, 0.9-2.8), which was reduced to 0.99 (95% CI, 0.6-1.6) at the time of European submission, suggesting that there are no major differences in the incidence of malignancies as compared to general population. Therefore, in the regulatory review in Europe, the applicant's assessment that "the diversity in the type of cancers observed, the relatively short duration of exposure and the clinical features of the individual cases render a causal relationship unlikely" was accepted, which was incorporated into the European labeling. On top of that, (a) the incidence of malignancies in clinical studies at the time of filing in Japan was 0.59% (31 of 5234 subjects) in the Omalizumab group and 0.23% (7 of 3087 subjects) in the control group and the standardized incidence ratio in the Omalizumab group was 0.98 (95% CI, 0.57-1.57), which were similar to those at the time of European submission. (b) According to the 3rd year interim report on EXCELS²⁰ (data cutoff date, November 30, 2007), the incidence was 2.0% in the Omalizumab group (102 of 5043 subjects) and 1.9% (54 of 2893 subjects) in the non-Omalizumab group, showing no significant difference between the groups. (c) According to the latest PSUR, the cumulative number of cases with malignancies reported up to the end of December 2007 was 286 (120 cases from post-marketing spontaneous reporting, 129 cases from post-marketing clinical studies, 36 cases from clinical studies, 1 case from the literature) and there has been no consistent trend in the type of malignancies. (d) Moreover, in non-clinical studies,

²⁰ Initially, patients with a history of malignancies or with a precancerous condition and patients assessed as having a potential diagnosis of cancer were excluded, but due to the FDA's request, the protocol was amended as of September 23, 2005 and these criteria were deleted.

there were no effects of Omalizumab on the immune system, nor has there been any report that IgE is involved in tumor development, growth, and metastasis. Based on the above data, we consider that there has been no evidence that Omalizumab increases the risk of malignancies.

PMDA has no objection to the applicant's current view, but considers that it is necessary to investigate the occurrence of malignancies via post-marketing surveillance etc. also in Japan and further define its risk based on the results of Japanese and foreign large-scale investigations.

4.(iii).B.(4).3 Risk of parasitic infections

PMDA asked the applicant to explain their view on the necessity of including a caution statement about the risk of parasitic infections also in the Japanese package insert since Foreign Study 2303 involving patients at high risk of parasitic infections showed an increased rate of reinfections with Omalizumab.

The applicant responded as follows:

Because IgE, the target ligand of Omalizumab, is considered to be one of the factors involved in the host defense against parasitic infections, Foreign Study 2303 was conducted in patients with allergic asthma or allergic rhinitis at high risk of parasitic infections (e.g. currently or previously infected with parasites) to investigate the risk of parasitic infections associated with Omalizumab, using the primary endpoint of the rate of intestinal parasitic infections after parasites were eliminated before the study drug administration. As a result, although the infection rate in the Omalizumab group (50.0% [34 of 68 subjects]) was slightly higher than that in the placebo group (40.6% [28 of 69 subjects]), there were no differences in the clinical course, severity, response to treatment of infection, etc. between the groups and an excessive increase of the risk of infections associated with Omalizumab was not suggested. In Japan, overall sanitary conditions are good and the consistent risk of parasitic infections seems low, but a potential increased risk of infections associated with Omalizumab cannot be excluded especially in areas where parasitic infections are endemic. Therefore, the following caution statement will be added to the Important Precautions section of the package insert: "Caution should be exercised for parasitic infections when travelling to areas where parasitic infections are endemic."

PMDA accepted the above response, but considers that it is necessary to continue to investigate the risk of parasitic infections associated with Omalizumab through post-marketing surveillance etc.

4.(iii).B.(4).4 Autoimmune disease

PMDA asked the applicant to explain the basis for denying a causal relationship to Omalizumab for 2 cases of systemic lupus erythematosus (SLE) observed in the Omalizumab group from foreign clinical studies and the potential for Omalizumab immune complexes to induce autoimmune disease.

The applicant explained as follows:

Although SLE was suspected in one case, a diagnosis of polyarthritis was made after work-up and a causal relationship of polyarthritis to Omalizumab was also denied. In the other case, SLE was reported after 3 doses of Omalizumab and treatment with Omalizumab was discontinued, but a rheumatologist assessed that it was likely that this subject had already had SLE before the start of the study. Immune complexes formed between Omalizumab and IgE following the administration of Omalizumab have small molecular weights (primarily about 500 kDa, up to about 1000 kDa), which cannot be a trigger for complement activation or a cause of disease induced by immune complexes.

PMDA considers as follows:

At present, the relationship between Omalizumab and autoimmune disease is unclear. However, taking into account that adverse events classified as autoimmune disease, e.g. rheumatoid arthritis and sarcoidosis, have been reported from overseas marketing experience, and considering the properties of Omalizumab as an antibody preparation, the possibility cannot be excluded that Omalizumab may cause immune disorders like other antibody preparations. Since immune disorders such as collagen disorder progress gradually, it is necessary to investigate the relationship between Omalizumab and immune disorders from a long-term perspective after the market launch.

4.(iii).B.(4).5 Safety in the elderly

PMDA asked the applicant to examine in detail the safety of Omalizumab in the elderly.

The applicant explained as follows:

In Japanese Study 1304, the incidence of adverse events was slightly higher in the Omalizumab group (92.6% [25 of 27 subjects]) than in the placebo group (85.7% [30 of 35 subjects]) among elderly subjects aged 65 or older and the System Organ Class (SOC) reported at a $\geq 5\%$ higher incidence in the Omalizumab group than in the placebo group was “Eye disorders” (Omalizumab group, 7.4% [2 of 27 subjects]; Placebo group, 0%), but a causal relationship to Omalizumab was denied for both events (lacrimation increased and vitreous floater). The SOCs reported at a $\geq 5\%$ higher incidence in the elderly than in the non-elderly in the Omalizumab group were “Investigations” and “Musculoskeletal and connective tissue disorders,” but there were no differences as compared with the elderly in the placebo group. In a pooled population from foreign placebo-controlled clinical studies (AAP population), the SOCs reported at a higher incidence in the elderly treated with Omalizumab than in the elderly treated with placebo and the non-elderly (aged between 18 and 64) treated with Omalizumab were “Cardiac disorders” (4.5% [3 of 67 subjects], 0%, and 0.6% [6 of 1046 subjects], respectively), “Eye disorders” (14.9% [10 of 67 subjects], 4.8% [2 of 42 subjects], and 5.2% [54 of 1046 subjects], respectively), and “Respiratory, thoracic and mediastinal disorders” (34.3% [23 of 67 subjects], 21.4% [9 of 42 subjects], and 25.1% [263 of 1046 subjects], respectively). Specifically, (a) concerning “Cardiac disorders,” 3 elderly subjects in the Omalizumab group experienced angina pectoris, coronary artery disease, and myocardial infarction, respectively, but coronary artery disease alone occurred in the elderly only and these subjects all had concurrent heart disease or the risk of

heart disease and their causal relationship to Omalizumab was denied. (b) Concerning “Eye disorders,” cataract (3 cases) was a frequently reported event in the elderly treated with Omalizumab and this event occurred only in the elderly treated with Omalizumab, but the primary cause of cataract is aging and a causal relationship to Omalizumab was denied for all cases, and there was no trend towards an increased incidence in the elderly for other events. (c) Concerning “Respiratory, thoracic and mediastinal disorders,” pharyngolaryngeal pain (10 cases) and cough (6 cases) were frequently reported in the elderly treated with Omalizumab, which were all mild to moderate and their causal relationship to Omalizumab was denied except for 1 case of cough. Moreover, with respect to all adverse events from overseas marketing experience accumulated in the safety database up to the end of July 2008, the percentage of events in each SOC was calculated by using the total numbers of events in the elderly and in the non-elderly as the denominators. As a result, compared to the non-elderly, the percentages of “Cardiac disorders” (1.93% [262 of 13576 events] and 4.99% [117 of 2347 events], respectively) and “Neoplasms benign, malignant and unspecified (including cysts and polyps)” (2.56% [348 of 13576 events] and 5.97% [140 of 2347 events], respectively) were slightly higher in the elderly, but there was no trend towards the occurrence of adverse events causing a particular concern about the use of Omalizumab in the elderly. Based on the interim report on a foreign post-marketing clinical study (EXCELS) (data cutoff at the end of November 2007), the main causes of deaths and serious adverse events classified as “Cardiac disorders” were compared between the elderly and non-elderly, which also showed no specific trend. Based on the above, there should be no major differences in the safety of Omalizumab between the elderly and other age groups.

Although PMDA accepts the above response at present, as the safety data from the elderly are limited, it is necessary to further investigate the safety in the elderly, based on Japanese post-marketing surveillance and overseas post-marketing safety data, etc.

4.(iii).B.(5) Post-marketing safety measures etc.

PMDA considers as follows:

The occurrence of anaphylaxis including delayed reactions associated with Omalizumab has been reported in foreign countries and it is necessary to fully investigate its occurrence also in Japan. Thrombocytopenia has been observed in non-clinical studies and the effects of Omalizumab on platelets in clinical use need to be further investigated. Omalizumab is a novel biopharmaceutical product with a new mode of action and it is necessary to further collect adequate information on its long-term safety, including the occurrence of malignancies. Therefore, a long-term, large-scale, post-marketing surveillance study to address these issues should be conducted. Since it is important to carefully determine the risks and benefits prior to the use of Omalizumab and ensure its proper use, the use of Omalizumab should be limited to physicians etc. with adequate knowledge about Omalizumab and experience in treatment of severe asthma. In order to promote the proper use of Omalizumab, it is necessary to provide information to healthcare providers and patients appropriately and promptly through the provision of detailed materials to healthcare providers such as physicians, the development of a patient information leaflet etc. describing the risks and benefits in an appropriate and

easy-to-understand manner, and the publication of the information obtained after the market launch on the Internet etc., whenever it becomes available.

Furthermore, it is also necessary to investigate the effect of Omalizumab in reducing asthma exacerbations by comparing the rate of asthma exacerbations before and after the administration of Omalizumab via post-marketing surveillance, so as to further define the clinical significance of Omalizumab.

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

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and reliability assessment

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

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.1-1, 5.3.5.1-1, 5.3.5.2-1-1, 5.3.5.4-2, 5.3.5.4-3, 5.3.5.4-4). As a result, it was found that at some clinical trial sites, in response to serious and unexpected adverse drug reactions etc. notified by the sponsor, the appropriateness of continuing the clinical trial was examined and deliberated by the institutional review board (IRB) through expedited review procedures and there were inconsistencies between the source documents and the CRF (failure to record adverse events and concomitant medications), but there were no major problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the application dossier.

IV. Overall Evaluation

The submitted data have shown a certain level of efficacy of Omalizumab in patients with bronchial asthma.

Regarding safety, because foreign clinical studies and post-marketing safety data have raised a concern about the development of anaphylaxis including delayed reactions, patients' symptoms should be carefully observed after the administration of Omalizumab and patients should also be informed of the signs and symptoms of anaphylaxis. After the market launch, it is necessary to conduct a large-scale, post-marketing surveillance study to further investigate the safety of its long-term use, including the occurrence of malignancies, and provide the obtained information etc. to physicians, patients, etc.,

whenever it becomes available.

Omalizumab may be approved for marketing if it can be concluded that there are no particular problems, taking account of comments from the Expert Discussion.

Review Report (2)

October 17, 2008

Taking account of comments from the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) conducted an additional review of the following points and took necessary actions. The relevant expert advisors have declared that no conflict of interest exists for the product submitted for registration, with regard to Section 1 and Section 2-(1) of “Tentative Rules for Addressing Conflict of Interest for the External Experts of the Pharmaceuticals and Medical Devices Agency” (as of May 8, 2007).

1. Proper use of Omalizumab

Based on comments from the Expert Discussion, PMDA requested the applicant to develop a guideline for the proper use of Omalizumab that describes the eligible patient population and a caution about adverse drug reactions such as anaphylaxis in order to ensure compliance with the proper use of Omalizumab. The applicant responded that they would address it promptly with the cooperation of the relevant academic societies etc. PMDA also requested the applicant to include the following statement in the package insert: “Omalizumab should be used under the supervision of physicians who are familiar with bronchial asthma.” The applicant accepted it.

2. Indication

PMDA considered that the INDICATION section should be modified as follows in order to specify the intended population for Omalizumab more clearly and asked the applicant to take an action. The applicant accepted it.

[Indication]

Bronchial asthma (only for refractory patients whose asthma symptoms are not controlled by conventional therapies)

3. Dosage and administration

PMDA instructed the applicant to include the dosing charts in the DOSAGE AND ADMINISTRATION section of the package insert and clearly state that dosing in a given cell of the dosing charts has been calculated to provide the recommended clinical dose of ≥ 0.008 mg/kg/[IU/mL] (every 2 weeks by subcutaneous injection) or ≥ 0.016 mg/kg/[IU/mL] (every 4 weeks by subcutaneous injection) of Omalizumab. The applicant responded that the DOSAGE AND ADMINISTRATION section would be modified as follows and PMDA accepted it.

[Dosage and administration]

The usual adult dosage is 75 to 375 mg of Omalizumab (Genetical Recombination) administered by subcutaneous injection every 2 or 4 weeks. Doses and dosing frequency are determined by serum total IgE level, measured before the start of treatment, and body weight, according to the dosing charts below.

Dosing charts (Dose for each administration)

Administration Every 4 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | |
|--|------------------|---------|---------|---------|---------|---------|---|-----------|--|
| | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| ≥ 30-100 | 75 mg | 150 mg | 150 mg | 150 mg | 150 mg | 150 mg | 300 mg | 300 mg | |
| > 100-200 | 150 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | Administration Every 2 Weeks See the table below | | |
| > 200-300 | 225 mg | 300 mg | 300 mg | | | | | | |
| > 300-400 | 300 mg | | | | | | | | |
| > 400-500 | | | | | | | | | |
| > 500-600 | | | | | | | | | |
| > 600-700 | | | | | | | | | |

Administration Every 2 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | |
|--|------------------------------|---------|---------|---------|---------|---------|-------------------|-----------|--|
| | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| ≥ 30-100 | Administration Every 4 Weeks | | | | | | | | |
| > 100-200 | See the above table | | | | | | 225 mg | 300 mg | |
| > 200-300 | | | | 225 mg | 225 mg | 225 mg | 300 mg | 375 mg | |
| > 300-400 | 225 mg | | 225 mg | 225 mg | 300 mg | 300 mg | Do not administer | | |
| > 400-500 | 225 mg | 225 mg | 300 mg | 300 mg | 375 mg | 375 mg | | | |
| > 500-600 | 225 mg | 300 mg | 300 mg | 375 mg | | | | | |
| > 600-700 | 225 mg | 300 mg | 375 mg | | | | | | |

Dosing in a given cell of the dosing charts has been calculated to provide the recommended clinical dose of ≥ 0.008 mg/kg/[IU/mL] (every 2 weeks by subcutaneous injection) or ≥ 0.016 mg/kg/[IU/mL] (every 4 weeks by subcutaneous injection) of Omalizumab.

4. Stability of the drug product

The data from the stability studies on the drug product that were ongoing at the time of filing were additionally submitted and the study results are as follows:

In the long-term testing on the drug product manufactured at a commercial scale by Genentech (partial vacuum) (5°C, 48 months), there were no changes from baseline in each attribute tested.

In the long term testing on the drug products (partial vacuum) manufactured by Novartis Pharma using the drug substance produced by Genentech and the drug substance produced by Novartis Pharma (5°C, 36 months for the drug product manufactured using the drug substance produced by Genentech, 24 months for the drug product manufactured using the drug substance produced by Novartis Pharma) and accelerated testing (partial vacuum, 30°C/65%RH, the drug product manufactured using the drug substance produced by Novartis Pharma, 6 months), both drug products were stable and there were no differences between the drug products manufactured using the drug substance produced by Genentech

and the drug substance produced by Novartis Pharma.

Based on the above, the applicant explained that because Novartis Pharma's product has comparable stability to Genentech's product, a proposed shelf life of the drug product of 4 years at 5°C when stored in glass vials has been justified.

PMDA accepted it.

5. Post-marketing surveillance etc.

PMDA instructed the applicant to design a post-marketing surveillance study that allows the applicant to investigate the occurrence of anaphylaxis/anaphylactoid reaction (anaphylaxis), thrombocytopenia, etc., collect safety data on long-term use, including the occurrence of malignancies, and assess the effect of Omalizumab in reducing asthma exacerbations.

The applicant responded as follows:

All treated patients will be enrolled in the study and the observation period is 1 year. The following requirements are to be met: Patients on continued treatment with Omalizumab will be followed up for up to another 3 years to collect information on the occurrence of malignancies; analysis will be performed when 3000 cases have been collected, but the study will be continued until the regulatory authority's final evaluation is obtained; the occurrence of anaphylaxis, bleeding tendency, malignancies, autoimmune disease, parasitic infections, etc. under routine drug uses will be identified; and the rate of asthma exacerbations will be compared before and after the administration of Omalizumab.

PMDA considers that the above study should be conducted promptly and the newly obtained information etc. should be provided to healthcare professionals as soon as possible.

As a result of the above review, PMDA has concluded that the product may be approved for marketing after modifying the indication and the dosage and administration as shown below. The re-examination period is 8 years, the drug substance and the drug product are classified as powerful drugs, and the product is classified as a biological product.

[Indication]

Bronchial asthma (only for refractory patients whose asthma symptoms are not controlled by conventional therapies)

[Dosage and administration]

The usual adult dosage is 75 to 375 mg of Omalizumab (Genetical Recombination) administered by subcutaneous injection every 2 or 4 weeks. Doses and dosing frequency are determined by serum total

IgE level, measured before the start of treatment, and body weight, according to the dosing charts below.

Dosing charts (Dose for each administration)

Administration Every 4 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | |
|--|------------------|---------|---------|---------|---------|---------|---|----------|--|
| | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | >125-150 | |
| ≥ 30-100 | 75 mg | 150 mg | 150 mg | 150 mg | 150 mg | 150 mg | 300 mg | 300 mg | |
| > 100-200 | 150 mg | 300 mg | 300 mg | 300 mg | 300 mg | 300 mg | Administration Every 2 Weeks See the table below | | |
| > 200-300 | 225 mg | 300 mg | 300 mg | | | | | | |
| > 300-400 | 300 mg | | | | | | | | |
| > 400-500 | | | | | | | | | |
| > 500-600 | | | | | | | | | |
| > 600-700 | | | | | | | | | |

Administration Every 2 Weeks

| Baseline serum total IgE level (IU/mL) | Body weight (kg) | | | | | | | | |
|--|------------------------------|---------|---------|---------|---------|---------|-------------------|-----------|--|
| | > 30-40 | > 40-50 | > 50-60 | > 60-70 | > 70-80 | > 80-90 | > 90-125 | > 125-150 | |
| ≥ 30-100 | Administration Every 4 Weeks | | | | | | | | |
| > 100-200 | See the above table | | | | | | 225 mg | 300 mg | |
| > 200-300 | | | | 225 mg | 225 mg | 225 mg | 300 mg | 375 mg | |
| > 300-400 | 225 mg | | 225 mg | 225 mg | 300 mg | 300 mg | Do not administer | | |
| > 400-500 | 225 mg | 225 mg | 300 mg | 300 mg | 375 mg | 375 mg | | | |
| > 500-600 | 225 mg | 300 mg | 300 mg | 375 mg | | | | | |
| > 600-700 | 225 mg | 300 mg | 375 mg | | | | | | |

Dosing in a given cell of the dosing charts has been calculated to provide the recommended clinical dose of ≥ 0.008 mg/kg/[IU/mL] (every 2 weeks by subcutaneous injection) or ≥ 0.016 mg/kg/[IU/mL] (every 4 weeks by subcutaneous injection) of Omalizumab.