**Report on the Deliberation Results**

December 2, 2016

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

| | |
|---|---|
| **Brand Name** | Otezla Tablets 10 mg |
| | Otezla Tablets 20 mg |
| | Otezla Tablets 30 mg |
| **Non-proprietary Name** | Apremilast (JAN*) |
| **Applicant** | Celgene K.K. |
| **Date of Application** | March 24, 2016 |

**Results of Deliberation**
In its meeting held on November 24, 2016, the Second 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 not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

**Condition of Approval**
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

**Review Report**

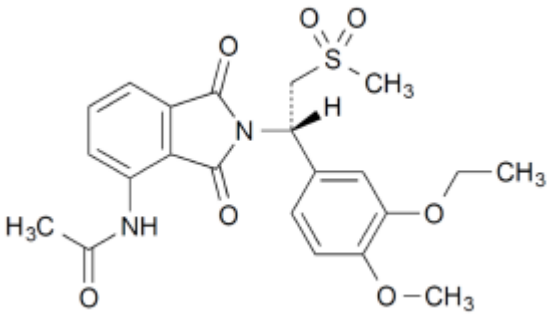
November 15, 2016

Pharmaceuticals and Medical Devices Agency

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

| | |
|---|---|
| **Brand Name** | Otezla Tablets 10 mg<br>Otezla Tablets 20 mg<br>Otezla Tablets 30 mg |
| **Non-proprietary Name** | Apremilast |
| **Applicant** | Celgene K.K. |
| **Date of Application** | March 24, 2016 |
| **Dosage Form/Strength** | Film-coated tablets, each containing 10 mg, 20 mg, or 30 mg of Apremilast |
| **Application Classification** | Prescription drug (1) Drug with a new active ingredient |

**Chemical Structure**



Molecular formula: $C_{22}H_{24}N_2O_7S$
Molecular weight: 460.50
Chemical name:

*N*-{2-[(1*S*)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide

**Reviewing Office** Office of New Drug IV

**Results of Review**
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of psoriasis vulgaris in patients who have had an inadequate response to topical therapy and psoriatic arthritis and that the product has acceptable safety in view of its benefit (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. The safety of the product in routine use should be further investigated in post-marketing surveillance.

**Indications**
Psoriasis vulgaris inadequately responding to topical therapy
Psoriatic arthritis

**Dosage and Administration**
The usual adult oral dose of Apremilast is shown below. From Day 6 onward, Apremilast is administered orally twice daily in the morning and evening at a dose of 30 mg.

| | Morning | Evening |
|---|---|---|
| Day 1 | 10 mg | - |
| Day 2 | 10 mg | 10 mg |
| Day 3 | 10 mg | 20 mg |
| Day 4 | 20 mg | 20 mg |
| Day 5 | 20 mg | 30 mg |
| Day 6 and thereafter | 30 mg | 30 mg |

**Condition of Approval**
The applicant is required to develop and appropriately implement a risk management plan.

**Attachment**

# Review Report (1)

October 25, 2016

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

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Otezla Tablets 10 mg<br>Otezla Tablets 20 mg<br>Otezla Tablets 30 mg |
| **Non-proprietary Name** | Apremilast |
| **Applicant** | Celgene K.K. |
| **Date of Application** | March 24, 2016 |
| **Dosage Form/Strength** | Film-coated tablets, each containing 10 mg, 20 mg, or 30 mg of Apremilast |
| **Proposed Indications** | Psoriasis vulgaris that is deemed inappropriate for topical therapy or that has been insufficiently responsive to topical therapy<br>Psoriatic arthritis |

**Proposed Dosage and Administration**

The usual adult oral dose of Apremilast is gradually increased according to the schedule shown below. From Day 6 onward, Apremilast is administered orally twice daily in the morning and evening at a dose of 30 mg.

Schedule for gradual dose increase

| | Morning | Evening |
|---|---|---|
| Day 1 | 10 mg | - |
| Day 2 | 10 mg | 10 mg |
| Day 3 | 10 mg | 20 mg |
| Day 4 | 20 mg | 20 mg |
| Day 5 | 20 mg | 30 mg |
| Day 6 and thereafter | 30 mg | 30 mg |

**Table of Contents**

**List of Abbreviations**

| | |
|---|---|
| ACR20 response rate, ACR50 response rate, ACR70 response rate | American College of Rheumatology 20, 50, 70 responder index |
| cAMP | Cyclic adenosine monophosphate |
| Apremilast | Apremilast |
| AUC | Area under concentration-time curve |
| BCRP | Breast cancer resistance protein |
| cAMP | Cyclic adenosine monophosphate |
| CASPAR | Classification criteria for psoriatic arthritis |
| CI | Confidence interval |
| CL | Clearance |
| $C_{max}$ | Maximum concentration |
| CREB | cAMP response element binding protein |
| CYP isoform | Cytochrome P450 isoform |
| DMARD | Disease-modifying antirheumatic drugs |
| FAS | Full Analysis Set |
| HLT | High level terms |
| HPLC | High performance liquid chromatography |
| $IC_{50}$ | Half maximal inhibitory concentration |
| IFN | Interferon |
| IL | Interleukin |
| ITT | intent-to-treat |
| LOCF | Last observation carried forward |
| LPS | Lipopolysaccharide |
| MACE | Major adverse cardiac events |
| mITT | modified Intent-to treat |
| MRP | Multidrug resistance-associated protein |
| NF-κB | nuclear factor-kappa B |
| NMR | Nuclear magnetic resonance spectrum |
| NRI | Non-responder imputation |
| OAT | Organic anion transporter |
| OATP | Organic anion transporting polypeptide |
| OCT | Organic cation transporter |
| Otezla | Otezla Tablets 10 mg, 20 mg, 30 mg |
| $P_{app}$ | Apparent permeability |
| PASI | Psoriasis area and severity index |
| PASI 75 response rate, PASI 90 response rate, PASI 100 response rate | Percentage of subjects achieving ≥75%, ≥90%, or ≥100% reduction form baseline in PASI score |
| PDE | phosphodiesterase |
| P-gp | P-glycoprotein |
| PKA | Protein kinase A |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PT | Preferred terms |
| PTP | Press through packaging |
| QTc | Corrected QT interval |
| RH | Relative humidity |
| SCQ | Sponsor Created Query |
| SMQ | Standardised MedDRA Queries |
| SOC | System Organ Class |
| sPGA | Static physician global assessment |
| Rate of achieving sPGA 0 or 1 | Percentage of subjects who had an sPGA score of 0 or 1 AND achieved improvement in the score by ≥2 points from baseline |
| $t_{1/2}$ | Elimination half-life |
| $t_{max}$ | Time to reach maximum concentration |
| TNF-α | Tumor necrosis factor alpha |
| UHPLC | Ultra High Performance Liquid Chromatography |
| Vd | Volume of distribution |
| β-NADPH | Beta-Nicotinamide Adenine Dinucleotide Phosphate |

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

Psoriasis, a chronic inflammatory skin disorder, is classified into psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, erythrodermic psoriasis, and guttate psoriasis by clinical symptoms. Psoriasis vulgaris, which is characterized by erythematous plaque with scale, is considered to account for approximately 90% of patients with psoriasis in Japan. Psoriatic arthritis is associated with inflammatory arthritis in addition to plaque rash.

Inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-23, and IL-17 in dermal and articular tissues are reported to be involved in the development and maintenance of the pathology of psoriasis (*Drug Discov Today*. 2005;10:1503-19, *Eur J Biochem*. 2002;269:4559-65). It is suggested that intracellular signal transduction mediated by transcription factors such as nuclear factor-kappa B (NF-κB) is involved in the production of these inflammatory cytokines (*N Engl J Med*. 2009;361:496-509). In clinical practice in Japan, topical agents such as corticosteroid and vitamin $D_3$ derivatives are used for patients with mild to moderate psoriasis, and systemic treatment with cyclosporine, etretinate, etc., and topical phototherapy are administered to patients with moderate to severe psoriasis in addition to the above topical agents. For patients who have had an inadequate response to these therapies, anti-TNF-α antibodies infliximab (genetical recombination) and adalimumab (genetical recombination), anti-IL-12/23 antibody ustekinumab (genetical recombination), and anti-IL-17 antibody secukinumab (genetical recombination) are used clinically.

Apremilast, the active ingredient of "Otezla Tablets 10 mg, 20 mg, and 30 mg (hereinafter referred to as Otezla)," is a compound containing phthalimide group which constitutes the chemical structure of thalidomide, lenalidomide, etc. The compound was discovered by Celgene Corporation (US). Among enzymes of the cyclic nucleotide phosphodiesterases (PDE) family which degrade intracellular second messengers cyclic nucleotides (cyclic adenosine monophosphate [cAMP], cGMP), apremilast inhibits cAMP-degrading PDE4 expressed mainly in immune cells, smooth muscle cells, and nerve cells (*Nat Rev Drug Discov*. 2014;13:290-314). It is suggested that compounds that inhibit PDE4 suppress the activation of cAMP-protein kinase A (PKA) - cAMP response element binding protein (CREB) pathway and the activation of NF-κB through PDE4 inhibition, thereby controlling the production of inflammatory cytokines in immune cells. Based on these findings, the development of Otezla, a product containing apremilast as the active ingredient, was initiated as a therapeutic agent for psoriasis and other inflammatory immune diseases.

In Japan, the development of Otezla for the treatment of psoriasis was initiated in [redacted] 20[redacted], and a clinical data package was constructed based on the "Ethnic Factors in the Acceptability of Foreign Clinical Data" (PMSB/ELD Notification No. 672 dated August 11, 1998). Now, a marketing application for Otezla in the proposed indication of psoriasis vulgaris and psoriatic arthritis has been submitted.

Otezla was approved in the US in March 2014 and in September 2014 for the indication for psoriatic arthritis and plaque psoriasis, respectively, and in Europe in January 2015 for the indication for both diseases. As of September 2016, Otezla is approved in 37 countries.

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

### 2.1 Drug substance

#### 2.1.1 Characterization

The drug substance is a white to pale yellow powder. The general properties of the drug substance, including description, specific rotation, solubility, acid dissociation constant and distribution coefficient, hygroscopicity, crystalline polymorphism, particle size distribution, and thermal analysis have been determined. During the development process, the drug substance was present in 7 different crystalline forms (Crystalline Forms A to G), but only Crystalline Form [redacted] is produced by the manufacturing process employed for the commercial production, and it has been confirmed that this crystalline form is stable at room temperature. In the final crystallization process, crystalline form measurement is the process control parameter to appropriately control the crystalline form.

The chemical structure of the drug substance has been elucidated by elementary analysis, infrared spectrophotometry, nuclear magnetic resonance spectrum (NMR) ($^{1}$H-NMR, $^{13}$C-NMR), ultraviolet and visible spectrophotometry, mass spectrometry, and single crystal X-ray diffractometry. The drug

substance contains one asymmetric carbon, and is synthesized as the *S*-isomer.

### 2.1.2 Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as the starting materials.

Based on following studies conducted using a quality-by-design approach, the strategy for quality control was constructed.

- Identification of residual solvents, related substances, enantiomer, and particle size as critical quality attributes
- Identification of critical step parameters based on the quality risk assessment and on the experimental design

Based on the results of the above investigations, the processes of the synthesis of [redacted] and [redacted] as well as the recrystallization process of the drug substance are identified as the critical steps. Also, [redacted] and [redacted] are controlled as critical intermediates in order to constantly ensure the quality of the drug substance.

During the review of the approval application, the starting material was changed from [redacted] to [redacted].

### 2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (infrared spectroscopy), purity (related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC], residual solvents [gas chromatography], and heavy metals), residue on ignition, particle size distribution, and assay (HPLC).

During the review process, purity (heavy metals) was added to the specifications for the drug substance.

### 2.1.4 Stability of drug substance

Table 1 shows the main stability studies conducted on the drug substance. A photostability testing showed that the drug substance was stable to light.

**Table 1. Stability studies of the drug substance**

| Study | Manufacturing process | Primary batch | Temperature | Humidity | Storage form | Storage period |
|---|---|---|---|---|---|---|
| Long-term testing | Process B[a)] | 3 pilot batches | 25°C | 60%RH | Low-density polyethylene bag (double-layered) + fiber drum | 48 months |
| | Process B[a)] | 6 pilot batches | 25°C | 60%RH | Low-density polyethylene bag (double-layered) + high-density polyethylene drum | 36 months[b)] |
| | Proposed manufacturing process | 3 commercial batches | 25°C | 60%RH | Low-density polyethylene bag (double-layered) + high-density polyethylene drum | 24 months[b)] |
| Accelerated testing | Process B[a)] | 3 pilot batches | 40°C | 75%RH | Low-density polyethylene bag (double-layered) + fiber drum | 6 months |
| | Process B[a)] | 3 pilot batches | 40°C | 75%RH | Low-density polyethylene bag (double-layered) + high-density polyethylene drum | 6 months[b)] |
| | Proposed manufacturing process | 3 commercial batches | 40°C | 75%RH | Low-density polyethylene bag (double-layered) + high-density polyethylene drum | 6 months[b)] |

a) The manufacturing process using the starting materials of [redacted] and [redacted] for synthesis. This method differs from the proposed manufacturing process in the process of isolating [redacted] from [redacted] under the condition of [redacted]. Results of batch analysis, etc., showed that there is no difference in the quality profiles between the drug substance manufactured by Process B and that manufactured by the proposed manufacturing process.

b) Only description, content, and purity (related substances) were investigated.

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored at room temperature in the double-layered low-density polyethylene bag placed in a high-density polyethylene drum. Long-term testing will be continued up to [redacted] months.

## 2.2 Drug product

### 2.2.1 Description and composition of the drug product and formulation development

The drug product is film-coated tablets, each containing 10 mg, 20 mg, or 30 mg of the drug substance. The drug product contains microcrystalline cellulose, lactose hydrate, croscarmellose sodium, magnesium stearate, and Opadry II (pink for 10-mg tablets, brown for 20-mg tablets, beige for 30-mg tablets), as excipients.

### 2.2.2 Manufacturing process

The drug product is manufactured through blending, tableting, coating, and packaging processes. [redacted] is identified as the critical step, and process control parameters and control values are defined for the process.

### 2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (ultraviolet-visible spectrophotometry and ultra high performance liquid chromatography [UHPLC]), purity (related substances [UHPLC]), uniformity of dosage unit (content uniformity [UHPLC]), dissolution (paddle method, UHPLC), and assay (UHPLC).

### 2.2.4 Stability of drug product

Table 2 shows the main stability studies performed on the drug product. A photostability test showed that the drug product is light-stable.

**Table 2. Stability of drug product**

| Study | Drug product | Primary batch | Temperature | Humidity | Storage form | Storage period |
|---|---|---|---|---|---|---|
| Long-term testing | 10-mg tablets | 3 pilot batches | 30°C | 65%RH | PTP packaging | 36 months |
| | 20-mg tablets | 3 pilot batches | | | | |
| | 30-mg tablets | 3 pilot batches | | | | |
| Accelerated testing | 10-mg tablets | 3 pilot batches | 40°C | 75%RH | | 6 months |
| | 20-mg tablets | 3 pilot batches | | | | |
| | 30-mg tablets | 3 pilot batches | | | | |

Based on the above, a shelf life of 36 months has been proposed for the drug product when packaged in press through packaging (PTP) (polyvinyl chloride film/aluminum foil) sheets and stored at room temperature.

## 2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

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

The applicant submitted the results from the primary pharmacodynamic studies, namely PDE-inhibitory effect of apremilast, effect on the inflammatory response of cells, and effects on animal models of inflammation. Also, the applicant submitted the results of secondary pharmacodynamic studies and safety pharmacology studies. In this section, pharmacological parameters are expressed in mean values unless specified otherwise.

## 3.1 Primary pharmacodynamics

### 3.1.1 Effect on PDE activity (CTD 4.2.1.1.1 to 4.2.1.1.3)

Using PDE1 (bovine), PDE2 (human platelets), PDE3 (human platelets), PDE4 (human monocyte-

derived U937 cells), PDE5 (human platelets), PDE6 (bovine retinal rod), PDE7 (human T cell-derived Hut78 cells), and PDE11 (human umbilical vein endothelial cells), the inhibitory effect of apremilast (maximum concentration 10 μmol/L) against the PDE family was investigated with cAMP hydrolysis as the index. Apremilast inhibited PDE4, PDE7, and PDE11 activities in a concentration-dependent manner with half maximal inhibitory concentration ($IC_{50}$) of 74, 20,500, and >100,000 nmol/L, respectively. On the other hand, the inhibition rate of apremilast at 10 μmol/L against PDE1, PDE2, PDE3, PDE5, and PDE6 was 23%, 6%, 20%, 3%, and −6%, respectively.

The inhibitory effect of apremilast (maximum concentration 10 μmol/L) against human PDE isozymes was investigated using cAMP hydrolysis as the index. The inhibition rate in the presence of apremilast 10 μmol/L was 3% (PDE1A), 5% (PDE1C), 5% (PDE2A), 4% (PDE3A), 12% (PDE3B), 96% (PDE4A1A), 96% (PDE4B1), 99% (PDE4B2), 91% (PDE4C1), 92% (PDE4D2), 0.2% (PDE5A1), 11% (PDE7A), 8% (PDE7B), 7% (PDE8A1), 0% (PDE9A2), 13% (PDE10A1), and 6% (PDE11A4). $IC_{50}$ of apremilast against human PDE4A1A, PDE4B1, PDE4B2, PDE4C1, PDE4D2, PDE4D3, and PDE4D7 was calculated to be 14, 43, 27, 118, 33, 28, and 30 nmol/L, respectively.

### 3.1.2 Effects on the expression of genes coding for inflammatory substances in various cells (CTD 4.2.1.1.7 and 4.2.1.1.8)

Using Jurkat T cells or THP-1 mononuclear cells, the effect of apremilast (0.1, 1, 10 μmol/L) on the activity of transcription factors CREB and NF-κB was investigated by Western blotting and luciferase assay. The Western blotting showed an increase in CREB phosphorylation in the presence of apremilast 1 or 10 μmol/L, and luciferase assay showed an increase in the transcriptional activity of CREB and inhibition of the transcriptional activity of NF-κB induced by TNF-α treatment, in the presence of apremilast 0.1 to 10 μmol/L.

Using human monocytes and human peripheral blood mononuclear cells, the effect of apremilast on lipopolysaccharide (LPS)-induced gene expression was investigated by gene expression analysis using gene chips. Apremilast (1 μmol/L) suppressed the expression of inflammatory substances such as CCL-2, CCL-7, CCL-8, CCL-15, CXCL-10, CXCL-11, interferon (IFN)-γ, IL-12/IL-23p40, IL-15, and TNF-α, while it enhanced the expression of amphiregulin (a member of epidermal growth factor family), bone morphogenetic protein, CD86, vascular endothelial growth factor, etc.

### 3.1.3 Effect on the production of inflammatory substances in various human cells (CTD 4.2.1.1.1, 4.2.1.1.10, 4.2.1.1.11, 4.2.1.1.13, 4.2.1.1.16, 4.2.1.1.17, and 4.2.1.1.34)

The effect of apremilast on the production of inflammatory cytokines in various human cells was investigated in *in vitro* systems. Table 3 summarizes the results.

**Table 3. Effect of apremilast on the production of inflammatory substances in various human cells**

| Cells | Stimulus | Apremilast concentration | Index substance such as cytokine | Results |
|---|---|---|---|---|
| Peripheral blood mononuclear cells | LPS (100 ng/mL) | 0.001-100 μmol/L | TNF-α, IL-10, IL-12 | $IC_{50}$ = 77 (TNF-α), 140 (IL-12) nmol/L. IL-10 production was enhanced. |
| | IL-1β (50 ng/mL) | | TNF-α | $IC_{50}$ = 83 nmol/L |
| | Staphylococcal enterotoxin B (100 ng/mL) | | IL-2, IFN-γ | $IC_{50}$ = 291 (IL-2), 46 (IFN-γ) nmol/L |
| CD4-positive helper T cells | Anti-CD3/CD28 antibody | | IL-5 | $IC_{50}$ = 890 nmol/L |
| Neutrophils | fMLP (1 μmol/L) | | Leukotriene B4 | $IC_{50}$ = 2.5 nmol/L |
| | Zymosan A (2.5 × $10^5$ particles) | | IL-8 | $IC_{50}$ = 94 nmol/L |
| Human peripheral blood mononuclear cells | LPS (4 ng/mL) | 0.0001-100 μmol/L | TNF-α, IL-12, GM-CSF, IL-8, IL-1β, IL-6, IL-10, etc. | $IC_{50}$ = 110 (TNF-α), 120 (IL-12), 7800 (GM-CSF) nmol/L. Neither IL-8 nor IL-1β was suppressed. IL-6 and IL-10 were increased. |
| Human whole blood | LPS (concentration unknown) | 0.5, 1.5 μmol/L | TNF-α, IL-12/23 p40, IP-10, MCP-1 | Production of all substances was suppressed by apremilast 0.5 and 1.5 μmol/L. |
| Human peripheral blood mononuclear cells | CpG-A oligodeoxynucleotide 2216 (1 or 10 μmol/L) | 0.00001-10 μmol/L | IFN-α, TNF-α | $IC_{50}$ = 620 (IFN-α), 120 (TNF-α) nmol/L. |
| Human plasmacytoid dendritic cells | | | | $IC_{50}$ = 480 (IFN-α), 270 (TNF-α) nmol/L. |
| Primary cultured human chondrocytes | Combination treatment with IL-1β (10 ng/mL), IL-6 (10 ng/mL), and IL-6 receptor (20 ng/mL) | 0.1-10 μmol/L | Expression of IL-7 mRNA and cell surface ICAM-1 and αVβ3 integrins | IL-7 mRNA expression was suppressed in a concentration-dependent manner. Expression of ICAM-1 and αVβ3 integrins was not suppressed. |
| Synovial fibroblasts derived from patients with rheumatoid arthritis | | | IL-7 mRNA expression | IL-7 mRNA expression was suppressed in a concentration-dependent manner. |
| Primary cultured human T cells | Anti-CD3 antibody (2.5 μg/mL) | 0.3-5000 ng/mL | IL-5, IL-17, IL-10, IL-13, TNF-α, GM-CSF, IFN-γ, IL-2 | $IC_{50}$ = 30 (IL-5), 90 (IL-17), 190 (IL-10), 280 (IL-13), 930 (TNF-α), 1000 (GM-CSF), 1300 (IFN-γ), 2400 (IL-2) nmol/L |
| Synovial cells derived from patients with rheumatoid arthritis | None | 6.25-100 nmol/L | TNF-α, IL-6 | $IC_{50}$ = 100 nmol/L (TNF-α). IL-6 production was not suppressed. |

fMLP: N-formyl-methionyl-leucyl-phenylalanine, GM-CSF: Granulocyte monocyte colony-stimulating factor

### 3.1.4 Effect on cyclooxygenase-2 (COX-2) enzyme (CTD 4.2.1.1.18 and 4.2.1.1.19)

Using human peripheral blood mononuclear cells, the effect of apremilast on LPS (1 ng/mL)-induced COX-2 protein expression and prostaglandin E2 production was investigated. Apremilast at 10 μmol/L enhanced LPS-induced COX-2 protein expression. Apremilast at 0.001 to 100 μmol/L enhanced LPS-induced prostaglandin E2 production in a concentration-dependent manner.

The effect of apremilast on the production of prostacyclin and thromboxane in platelet-treated human umbilical vein endothelial cells or in calcium ionophore-treated platelets was investigated. Apremilast at 0.00001 to 10 μmol/L had no effect.

### 3.1.5 Effect on neovascularization (CTD 4.2.1.1.1, 4.2.1.1.20, and 4.2.1.1.21)

Human umbilical vein endothelial cells were treated with vascular endothelial growth factor or fibroblast growth factor, after which the cells were added to apremilast (0.01-100 μmol/L), and the effect of apremilast on cell growth was investigated using thymidine uptake as the index. Apremilast suppressed vascular endothelial growth factor-induced cell growth in a concentration-dependent manner with $IC_{50}$ of 6.7 μmol/L, while it did not affect fibroblast growth factor-induced cell growth.

Human umbilical cords were treated with apremilast (0.1-100 μmol/L). Apremilast inhibited neovascularization in the human umbilical cords in a concentration-dependent manner with $IC_{50}$ of 0.14 μmol/L.

Using human umbilical vein endothelial cells, the effect of apremilast on IL-1β (50 ng/mL)-induced nitric oxide production was investigated. Apremilast at 10 μmol/L suppressed IL-1β-induced nitric oxide production by 87%.

### 3.1.6 Effect on osteoclast formation (CTD 4.2.1.1.23)

Using human bone marrow mononuclear cells, the effect of apremilast (0.1, 1, 10 μmol/L) on vitamin D- or dexamethasone-induced osteoclast formation was investigated. Apremilast suppressed osteoclast formation in a concentration-dependent manner. A decrease in the expression of sRANKL (soluble receptor activator of NF-κB ligand) was observed in all apremilast-treated groups, and an increase in the expression of BMP-6 (bone morphogenetic protein-6) was observed in the apremilast 10 μmol/L group.

### 3.1.7 Effect on cytokine production (CTD 4.2.1.1.12)

Using whole blood samples collected from rats, mice, monkeys, and humans, the effect of apremilast (0.01-10 μmol/L) on LPS-induced IL-6 production was investigated. Apremilast increased IL-6 production in the LPS (10 μg/mL)-treated whole blood of rats and mice in a concentration-dependent manner. Apremilast suppressed IL-6 production in the LPS (1 ng/mL)-treated whole blood of monkeys in a concentration-dependent manner. In contrast, apremilast had no effect on IL-6 production in LPS (1 ng/mL)-treated whole blood of humans.

### 3.1.8 Effect of metabolites on PDE4 activity and TNF-α production (CTD 4.2.1.1.24 to 4.2.1.1.27)

Using U937 human monocyte cells, the effect of the metabolites of apremilast (M1/M2, M3, M5, M7, M12, M14, M16, M17; See "4.3 Metabolism") on PDE4 activity was investigated with cAMP hydrolysis as the index. Using human peripheral blood mononuclear cells, the effect of the metabolites on LPS (1 ng/mL)-induced TNF-α production was investigated. Results are shown in Table 4, which suggests that M7 and M17 inhibit PDE4 activity. However, since the concentrations of M7 and M17 in plasma are both <1% of plasma apremilast concentration, the applicant discussed that the pharmacological contribution of the metabolites is limited.

**Table 4. Effect of the metabolites of apremilast on PDE4 activity and TNF-α production**

| Apremilast or metabolite | Effect on PDE4 activity $IC_{50}$ (μmol/L) | Effect on TNF-α production $IC_{50}$ (μmol/L) |
|---|---|---|
| Apremilast | 0.074 | 0.077 |
| M1/M2 (ring-opening hydrolysate) | 120 | 77 |
| M3 (*O*-desmethylate) | 8.3 | 5.6 |
| M5 (*O*-desethylate) | 44 | 4.9 |
| M7 (*N*-deacetylate) | 0.16 | 0.13 |
| M12 (*O*-desmethyl glucuronide) | >100 | >10 |
| M14 (*N*-deacetyl *O*-desmethyl glucuronide) | >80 | >10 |
| M16 (acetamide-hydroxy-glucuronide) | 6.5 | >10 |
| M17 (acetamide-hydroxy) | 0.094 | 0.021 |

M5 is a racemate. Other metabolites are *S*-enantiomers.

### 3.1.9 Effect on animal models of acute inflammatory reaction (CTD 4.2.1.1.1 and 4.2.1.1.28)

An animal model of acute inflammatory reaction was generated by intraperitoneal administration of LPS to mice, and the effect of oral administration of apremilast (0.01, 0.1, 1 mg/kg) in these animals was investigated. Apremilast suppressed the increase in serum TNF-α concentration induced by LPS in a concentration-dependent manner.

In an animal model of acute inflammatory reaction generated by intravenous administration of LPS (20 μg) to rats, the increase in serum TNF-α was suppressed by oral administration of apremilast (0.01-10 mg/kg).

### 3.1.10 Effect on rat model of carrageenan-induced hyperalgesia (CTD.4.2.1.1.30)

An animal model of inflammatory hyperalgesia was generated by subcutaneous administration of 1% carrageenan to rat legs, and the effect of intraperitoneal administration of apremilast (50 mg/kg) in these animals was investigated. Apremilast increased the pain threshold which had been decreased by carrageenan administration, and suppressed footpad edema.

### 3.1.11 Effect on animal models of arthritis (CTD 4.2.1.1.32, 4.2.1.1.33, 4.2.1.1.35, and 4.2.1.1.36)

A mouse model of arthritis was generated by intradermal administration of type II collagen and complete Freund's adjuvant, followed by subcutaneous administration of LPS after 21 days, and the effect of 14-day repeated oral administration of apremilast (1, 10 mg/kg) in these animals was investigated. Apremilast suppressed footpad edema in the animal model of arthritis. Also, 17-day repeated oral administration of apremilast (5, 25 mg/kg) decreased arthritis symptom score in the same animal model.

A mouse model of arthritis was generated by intracutaneous administration of type II collagen and complete Freund's adjuvant, followed by intraperitoneal administration of type II collagen after 21 days, and the effect of repeated oral administration of apremilast (10 mg/kg) and repeated intraperitoneal administration of etanercept (genetical recombination, 10 mg/kg) in these animals was investigated.[1)] Apremilast and etanercept (genetical recombination) both decreased arthritis symptom score. On the other hand, neither apremilast nor etanercept (genetical recombination) had an effect on the increase in the percentage of Th17 cells in the groin lymph nodes. Apremilast increased serum IFN-γ and IL-6 concentrations.

A mouse model of arthritis was generated by intravenous administration of a cocktail of 4 types of anti-collagen antibodies, followed by intraperitoneal administration of LPS after 3 days, and the effect of 5-day repeated oral administration of apremilast (1, 5, 25 mg/kg) in these animals was investigated. Apremilast at 25 mg/kg decreased arthritis symptom score and attenuated the arthritic findings (synovial hyperplasia, infiltration of inflammatory cells into the synovial membrane, fibrin deposition, cartilage destruction, etc.).

1) Apremilast or etanercept (genetical recombination) was administered every day from the day of intracutaneous administration of type II collagen and complete Freund's adjuvant.

### 3.1.12 Effect on mouse model of dermatitis psoriasiform (CTD 4.2.1.1.39)

A mouse model showing psoriasis-like symptoms was generated by transplanting a skin slice of a healthy adult to beige-severe combined immunodeficiency mice, followed by treatment with natural killer cells of a patient with psoriasis after 28 days (*AM J Pathol*. 1995;146:580-8, *J Clin Invest*. 1996;98:1878-87). The effect of repeated oral administration of apremilast (5 mg/kg) or cyclosporine (5 mg/kg) on the psoriasis-like symptoms in these animals was investigated. Apremilast suppressed skin lesion findings (hyperkeratosis, parakeratosis, and lymphocyte infiltration), epidermis thickness, keratinocyte growth, and expression of TNF-α and intercellular adhesion molecules, etc., in the skin graft in the mouse model showing psoriasis-like symptoms to a similar extent as those observed with cyclosporine.

### 3.1.13 Effect on apoptosis in mouse skin induced by UV irradiation (CTD 4.2.1.1.40)

The effect of oral administration of apremilast (25 mg/kg) on UV irradiation-induced apoptosis was investigated in hairless mice using DNA damage detected by TUNEL (TdT-mediated dUTP nick end labeling) staining as the index. When apremilast was orally administered 1 hour before UVB irradiation, the number of TUNEL-positive cells induced by UVB irradiation was smaller compared with the vehicle control, suggesting that apremilast suppressed apoptosis in the epidermis.

### 3.1.14 Effect on acquired immune response in mice (CTD 4.2.1.1.42)

Antigen-specific T cells recognizing hen egg-white lysozyme antigen or antigen-specific B cells recognizing ovalbumin antigen were administered intravenously to mice and, on the next day, egg-white lysozyme or ovalbumin was administered subcutaneously to activate immune response. The effect of repeated oral administration of apremilast (5 mg/kg) on the activated immune response was investigated in these animals. When apremilast was administered for 14 days from the day of the administration of the antigen-specific T or B cells, apremilast had no effect on the growth of T or B cells, expression of T cell-activation markers (CD69, CD25), expression of B cell-activation markers (CD40, CD86), or production of immunoglobulins such as IgG1, IgG2, or IgMa.

## 3.2 Secondary pharmacodynamics

### 3.2.1 Effect on receptors, enzymes, and transporters (CTD 4.2.1.1.4 to 4.2.1.1.6)

The effect of apremilast (10 μmol/L) on receptors, ion channels, enzymes, and transporters was investigated. Apremilast caused a 52% increase in the binding of radioactive ligand [$^3$H]D888 to the verapamil binding site of L-type calcium channel receptor. Based on this result, the effect of apremilast (0.01-30 μmol/L) on [$^3$H]D888 binding was investigated using L-type calcium channel receptor derived from rat cerebral cortex for a longer reaction time. Apremilast (0.01-30 μmol/L) had no effect on the binding of [$^3$H]D888. Since the additional study did not show the concentration-dependent effect of apremilast, the applicant explained that apremilast has little, if any, effect on calcium channel. Apremilast had no effect on other receptors, ion channels, enzymes, or transporters investigated.

### 3.2.2 Binding to human cerebron (CTD 4.2.1.2.1)

Taking account of the facts that apremilast contains phthalimide group which constitutes the chemical structure of thalidomide, lenalidomide, etc., and that cerebron, the coreceptor of E3 ubiquitin ligase substrate, is identified as the molecule responsible for the teratogenicity of thalidomide (*Science*. 2010;327:1345-50), binding of apremilast to human cerebron was investigated. Thus, the competitive inhibitory effect of apremilast against the binding of cerebron to a thalidomide analog immobilized on beads was investigated. Apremilast (0.1-100 μmol/L) did not inhibit the binding of cerebron.

### 3.2.3 Emetic effect (CTD 4.2.1.2.3)

A single dose of apremilast (0.1-30 mg/kg) was administered orally to ferrets to evaluate the emetic effect of apremilast. Vomiting occurred in the apremilast 30 mg/kg group but not in the apremilast 0.1 to 10 mg/kg groups.

## 3.3 Safety pharmacology

### 3.3.1 Effect on the central nervous system (CTD 4.2.1.3.1)

Following a single oral administration of apremilast (500, 1000, 2000 mg/kg) to male mice (n = 6/group), the effect on clinical conditions and behavior was investigated by modified Irwin's method. No findings were observed in the apremilast 500 mg/kg group, whereas a mild transient lacrimation and ptosis were

observed in the apremilast 1000 mg/kg group and, in the apremilast 2000 mg/kg group, 1 animal died at 2 days after administration, 1 animal showed piloerection, and other animals showed mild and transient indifference, lacrimation, and ptosis. Maximum concentration ($C_{max}$) and area under concentration-time curve (AUC) of apremilast after oral administration at 500 mg/kg were 8650 ng/mL and 112,640 ng·h/mL, respectively (CTD 4.2.3.2.1), which were approximately 26 and 21 times, respectively, larger than $C_{max}$ (334 ng/mL) and AUC (estimated, 5332 ng·h/mL) observed following twice daily multiple dosing of apremilast (30 mg) to Japanese patients with psoriasis.

### 3.3.2 Effect on human ether-a-go-go related gene (hERG) current (CTD 4.2.1.3.3)

Using human fetal kidney-derived 293 cell expressing *hERG* gene, the effect of apremilast (16.8-249.7 μmol/L) on hERG current was investigated by the patch-clamp method. Apremilast inhibited hERG current in a concentration-dependent manner with $IC_{50}$ of 184.2 μmol/L, which was approximately 254 times that observed after twice daily multiple dosing of apremilast (30 mg) to Japanese patients with psoriasis (334 ng/mL).

### 3.3.3 Effect on cardiovascular system and respiratory system (CTD 4.2.1.3.2)

A single dose of apremilast (0.5, 1, 5 mg/kg) was administered intravenously to male and female dogs (n = 2/sex/group), and the effect on cardiac function and respiratory function was investigated. As for the cardiac function, apremilast (0.5 mg/kg) caused a mild and tentative increase (by 9%) in $dP/dt_{max}$, but had no effect on other cardiac function parameters such as blood pressure. Apremilast (1 and 5 mg/kg) increased heart rate by 28% and 82% respectively, and $dP/dt_{max}$ by 29% and 74%, respectively, and the effects persisted throughout the observation period. Apremilast (1 and 5 mg/kg) caused a decrease in heartbeat interval and QT interval, but had no effect on corrected QT (QTc) interval. As for respiratory function, apremilast (5 mg/kg) caused a mild and tentative increase in peak inspiratory flow, but did not affect respiratory depth or respiratory rate at any doses. $C_{max}$ of apremilast was 662, 1277, and 5074 ng/mL, respectively, in the 0.5, 1, and 5 mg/kg groups, which was approximately 2, 4, and 15 times, respectively, higher than that following twice daily multiple dosing of apremilast (30 mg) in Japanese patients with psoriasis (334 ng/mL). Although a mild effect on heart rate and ventricular contractility was observed in the apremilast ≥1.0 mg/kg groups, the applicant explained that there are no particular safety problems because no effect on QTc interval was observed and apremilast had no effect on QT/QTc in humans [see "6.2.6.1 Effect on QTc interval"].

### 3.3.4 Effect on gastrointestinal transport (CTD 4.2.1.3.4)

A single dose of apremilast (10, 100, 1000 mg/kg) was administered orally to male mice (n = 6/group), after which a suspension of activated carbon was administered orally. Apremilast had no effect on the transferred distance of the activated carbon in the gastrointestinal tract in any treatment groups.

## 3.R Outline of the review conducted by PMDA

### 3.R.1 Efficacy of apremilast in psoriasis

The applicant's explanation on the mechanism of action and efficacy of apremilast against psoriasis:
PDE4 is expressed mainly in immune cells such as dendritic cells, monocytes, macrophages, neutrophils, T cells, B cells, keratinocytes, chondrocytes, and synoviocytes (*Curr Pharm Des*. 2002;8:1255-96). Under the pathological conditions of psoriasis vulgaris and psoriatic arthritis, PDE4 in immune cells of the affected sites is activated, thereby enhancing the activity of transcription factor NF-κB, and that this causes enhanced production of inflammatory mediators such as TNF-α, IL-17, and IL-23 and suppressed production of anti-inflammatory cytokines such as IL-10, precipitating into the pathology of psoriasis (*Drug Discov Today.* 2005;10:1503-19, *Eur J Biochem.* 2002;269:4559-65).

In the primary pharmacodynamic studies, apremilast selectively inhibited PDE4 and suppressed the expression of inflammatory cytokines in various cellular systems. These results suggest that apremilast exhibits its effect on psoriasis by controlling the overproduction of inflammatory cytokines. In addition, apremilast demonstrated its effectiveness in animal models of dermatitis psoriasiform and arthritis, from which apremilast is expected to be effective against psoriasis vulgaris and psoriatic arthritis.

Taking account of the observations that IL-6 production was increased when human peripheral blood mononuclear cells were treated with apremilast and that serum IL-6 and IFN-γ concentrations were increased by apremilast in the mouse models of arthritis, PMDA asked the applicant to explain the roles

these inflammatory cytokines play in the pathology of psoriasis and to interpret the results of these nonclinical studies.

The applicant's explanation:
TGF-β and IL-6 play important roles in inducing differentiation of T cells into Th17 cells which produce IL-17, a cytokine that plays a central role in the pathology of psoriasis (*J Invest Dermatol*. 2013;33:17-26). Also, it is reported that, in patients with psoriasis vulgaris, IFN-γ produced by skin residential T cells induces the expression of chemokines such as CXCL10 in epidermal keratinocytes *(Annu Rev Immunol.* 2014;32:227-55). Thus, the possibility cannot be ruled out that IL-6 and IFN-γ are involved in the pathology of psoriasis. However, apremilast concentration that caused an increase in IL-6 production in human peripheral blood mononuclear cells was 10 μmol/L, which was approximately 14 times the exposure ($C_{max}$, 334 ng/mL [ca. 0.7 μmol/L]) observed following twice daily multiple dosing of apremilast (30 mg) in Japanese patients with psoriasis. In the mouse model of arthritis, IL-6 and IFN-γ increased only after repeated dose of apremilast at 10 mg/kg/day, whereas in the foreign phase III studies (Studies CC-1004-PSOR-009 and CC-10004-PSA-002), apremilast did not cause any increase in plasma IL-6 or IFN-γ concentration. These results suggest that the increases in plasma IL-6 and IFN-γ concentrations observed in the nonclinical pharmacology studies occur at a higher apremilast concentration than that achieved by the clinical dose and therefore that the increases in these cytokines are unlikely to affect the efficacy of apremilast.

PMDA accepted the explanation of the applicant.

### 3.R.2 Effect of apremilast on safety associated with its immunosuppressive action

Taking account of the effect of apremilast on the immune system, the applicant explained the safety from a pharmacological point of view, as follows:
Apremilast is considered to suppress the expression of various inflammatory cytokines through PDE4 inhibition. However, unlike the anti-TNF-α drug etanercept (genetical recombination), apremilast did not completely suppress TNF-α production in studies with immune cells, as shown in Figure 1. Also, as shown in Table 5, when apremilast (30 mg) was administered twice daily for 52 weeks to Japanese patients with psoriasis, plasma IL-17A, IL-17F, IL-22, TNF-α concentrations were suppressed by 60.9%, 68.7%, 48.1%, and 34.8%, respectively, from baseline, but the suppressions were incomplete, with their plasma concentrations remaining within the concentration range in healthy adults. The above results suggest that apremilast does not completely suppress the immune function; it suppresses the expression of inflammatory cytokines only partially. Therefore, apremilast is unlikely to affect normal immune function and is unlikely to have a potential risk of immune system-related adverse events such as infection.

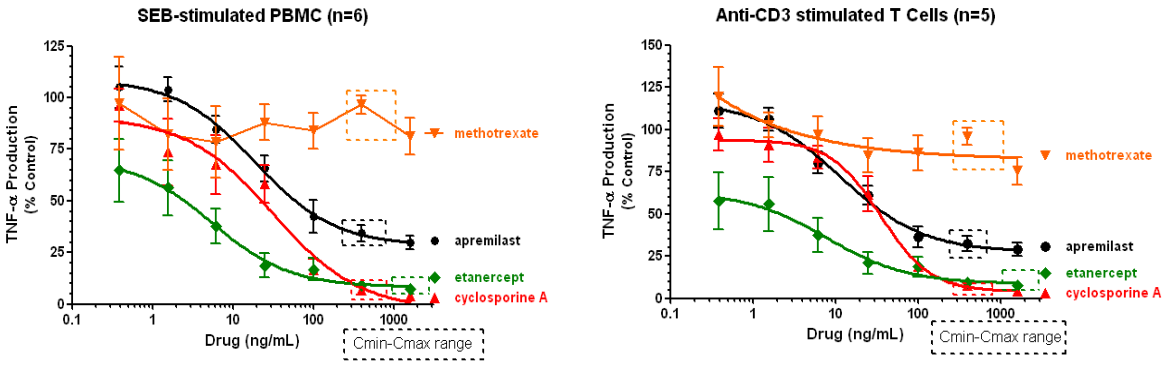



**Figure 1. Effect of various drugs on TNF-α production in human peripheral blood mononuclear cells after treatment with Staphylococcal enterotoxin B (left) and on TNF-α production in T cells treated with anti-CD3 antibody (right) (minimum blood concentration-maximum blood concentration, the range of plasma concentration following the administration of apremilast at clinical dose)**

**Table 5. Changes in plasma cytokine concentrations over time in patients with psoriasis**

| | | | Study CC-10004-PSOR-011 (Japanese) | | Study CC-10004-PSOR-009 (non-Japanese) | |
|---|---|---|---|---|---|---|
| Cytokine | Range in healthy adults[a)] | Measuring time point | Placebo (n = 23) | Apremilast 30 mg BID (n = 24) | Placebo (n = 47) | Apremilast 30 mg BID (n = 82) |
| IL-17A (pg/mL) | 0.1-1.93 | Baseline | 1.9 ± 1.3 | 1.6 ± 1.4 | 2.0 ± 5.2 | 1.8 ± 4.7 |
| | | Week 16 | 2.1 ± 1.3 | 0.88 ± 0.74 | 1.3 ± 2.0 | 0.63 ± 0.83 |
| | | Week 52 | - | 0.62 ± 0.56 [b)] | - | 0.63 ± 0.74 [c)] |
| IL-17F (pg/mL) | 0.28-1.95 | Baseline | 12.2 ± 11.9 | 9.9 ± 9.2 | 4.4 ± 3.9 | 5.3 ± 8.4 |
| | | Week 16 | 16.5 ± 23.0 | 3.6 ± 2.8 | 3.4 ± 3.5 | 2.2 ± 3.2 |
| | | Week 52 | - | 2.9 ± 2.6 [b)] | - | 3.2 ± 9.6 [c)] |
| IL-22 (pg/mL) | 1.6-6.9 | Baseline | 30.3 ± 23.0 | 21.7 ± 19.8 | 16.6 ± 23.9 | 18.4 ± 33.5 |
| | | Week 16 | 36.5 ± 47.8 | 10.7 ± 5.8 | 11.6 ± 11.8 | 9.5 ± 14.3 |
| | | Week 52 | - | 9.5 ± 7.8 [b)] | - | 10.6 ± 30.9 [c)] |
| TNF-α (pg/mL) | 0.5-2.53 | Baseline | 15.9 ± 40.2 | 5.7 ± 1.7 | 4.2 ± 2.4 | 4.4 ± 5.1 |
| | | Week 16 | 13.3 ± 21.3 | 5.5 ± 1.7 | 4.1 ± 1.9 | 3.8 ± 3.5 |
| | | Week 52 | - | 4.0 ± 1.9 [b)] | - | 3.2 ± 1.1 [c)] |

Mean ± standard deviation (SD); BID, Twice daily
a) *Cytokine.* 2013;64:660-5, *Bioanalysis.* 2016;8:2317-27, *J Immunol Methods.* 2013;390:30-5
b) n = 22
c) Measured at Week 44

While the applicant's explanation is understandable, PMDA considers that the safety of apremilast should be evaluated with the occurrences of infections in clinical studies into account.

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

The applicant submitted data on the absorption, distribution, metabolism, excretion, and drug interactions of apremilast, namely the results from studies on oral and intravenous administration in mice, rats, rabbits, and monkeys. Pharmacokinetics was investigated using apremilast or $^{14}$C-labeled apremilast. Plasma apremilast concentration was measured by high-performance liquid chromatography-tandem mass spectrometry (lower limit of quantitation; 2-75 ng/mL [achiral], 1 ng/mL [chiral]). Radioactivity concentrations in plasma, urine, feces, and bile were measured by a liquid scintillation counter or liquid chromatography with a radiodetector.

Pharmacokinetic parameters are expressed in mean or mean ± standard deviation (SD) unless specified otherwise.

### 4.1 Absorption

#### 4.1.1 Single-dose administration (CTD 4.2.2.2.1, 4.2.2.2.2, 4.2.2.2.6, and 4.2.2.2.8)

Table 6 shows pharmacokinetic parameters following a single-dose administration of apremilast to male and female mice, male and female rats, and female rabbits.

Following a single oral or intravenous administration of apremilast to male and female rats, the exposure tended to be higher in females than in males, and the absolute bioavailability was 11.5% in males and 64.8% in females. Regarding the higher tendency of the exposure in females, the applicant explained that the sex difference in cytochrome P450-mediated metabolism was likely to have caused the observed difference, from the following reasons: (1) In the study using rat liver-derived microsomes, M3, an oxidative metabolite of apremilast which was suggested to be generated as a result of cytochrome P450-mediated metabolism, was observed only in male rats [see "4.3.1.1 Studies with liver microsomes"], and (2) following a single oral administration of $^{14}$C-apremilast (10 mg/kg), the percentage of M3 in urine and feces at 12 hours after administration was 0.02% and 26.4%, respectively, in male rats, whereas M3 level was below the lower detection limit and 0.06%, respectively, in female rats (CTD 4.2.2.2.3).

Following a single oral administration of $^{14}$C-apremilast (10 mg/kg) to male and female monkeys, the radioactivity was rapidly absorbed into the body with the absorption rate being 81.0% to 93.2%, as calculated by comparison with the data obtained following a single intravenous administration of $^{14}$C-apremilast (1 mg/kg). In contrast, when a single dose of $^{14}$C-apremilast (1 mg/kg) was administered intravenously to monkeys, plasma apremilast concentration decreased below the lower limit of quantitation within 30 minutes after administration, precluding pharmacokinetic analysis.

**Table 6. Pharmacokinetic parameters following a single-dose administration of apremilast**

| Animal species | Mice | | | | Rats | | | |
|---|---|---|---|---|---|---|---|---|
| Dose and route of administration | 10 mg/kg i.v. | | 500 mg/kg p.o. | | 5 mg/kg i.v. | | 50 mg/kg p.o. | 10 mg/kg p.o. |
| Sex | Male | Female | Male | Female | Male | Female | Male | Female |
| No. of animals | 39 each[a)] | | 36 each[a)] | | 3 each | | 3 each | |
| $C_{max}$ (μg/mL) | 7.5[b)] | 7.3[b)] | 16.3 | 13.3 | 3.2 ± 1.2[b)] | 6.6 ± 1.8[b)] | 0.5 ± 0.1 | 1.1 ± 0.2 |
| $AUC_t$ (μg·h/mL) | 15.3 | 18.0 | 209 | 195 | 2.0 ± 0.9 | 11.5 ± 2.2 | 2.3 ± 0.5 | 13.5 ± 1.8 |
| $AUC_{inf}$ (μg·h/mL) | 15.9 | 18.4 | 227 | 242 | 1.9 ± 0.9 | 11.4 ± 2.3 | 2.2 ± 0.5 | 14.2 ± 1.5 |
| $t_{max}$ (h) | - | - | 1 | 4 | - | - | 4.0 ± 2.0 | 6.0 ± 3.5 |
| $t_{1/2}$ (h) | 1.7 | 2.3 | 15.5 | 21.9 | 0.6 ± 0.3 | 2.7 ± 0.4 | 1.6 ± 0.4 | 5.1 ± 2.3 |
| Vd (L/kg) | 1.5 | 1.8 | - | - | 2.1 ± 0.3 | 1.8 ± 0.2 | - | - |
| CL (L/h/kg) | 0.63 | 0.54 | - | - | 2.9 ± 1.0 | 0.5 ± 0.1 | - | - |
| BA (%) | - | - | 28.5[c)] | 26.3[c)] | - | - | 11.5[c)] | 64.8[c)] |

| Animal species | Pregnant rabbits | | Monkeys | |
|---|---|---|---|---|
| Dose and route of administration | 10 mg/kg i.v. | 250 mg/kg p.o. | 10 mg/kg p.o. | |
| Sex | Female | Female | Male | Female |
| No. of animals | 3 each | | 3 each | |
| $C_{max}$ (μg/mL) | 4.2 ± 0.8[d)] | 0.003 ± 0.001 | 2.0 ± 0.5 | 2.3 ± 0.2 |
| $AUC_t$ (μg·h/mL) | 4.9 ± 0.7 | 0.014 ± 0.013 | 7.5 ± 1.1 | 8.1 ± 1.7 |
| $AUC_{inf}$ (μg·h/mL) | 4.9 ± 0.7 | - | 7.8 ± 1.2 | 8.3 ± 1.8 |
| $t_{max}$ (h) | - | 5.0 ± 3.6 | 1.2 ± 0.7 | 1.2 ± 0.8 |
| $t_{1/2}$ (h) | 1.2 ± 0.2 | - | 2.0 ± 0.5 | 1.7 ± 0.6 |
| Vd (L/kg) | 1.8 ± 0.3 | - | - | - |
| CL (L/h/kg) | 2.0 ± 0.3 | - | - | - |
| BA (%) | - | 0.012[e)] | - | - |

Mean or mean ± SD; -, Not calculated; i.v., Intravenous administration; p.o., Oral administration; BA, Absolute bioavailability
a) Measured in 3 animals at each measuring time point
b) Measured at 5 minutes after administration
c) Calculated from $AUC_{inf}$
d) Measured at 1 hour after administration
e) Calculated from $AUC_t$

### 4.1.2 Repeat-dose administration (toxicokinetics) (CTD 4.2.3.2.5 to 4.2.3.2.8, 4.2.3.2.12, and 4.2.3.2.13)

The exposure to apremilast following repeat-dose administration was investigated by toxicokinetics. Table 7 shows the results. Repeat-dose administration did not cause accumulation of apremilast in any animal species studied.

**Table 7. Pharmacokinetic parameters following repeat-dose administration of apremilast**

| Animal species | Treatment duration | Dose (mg/kg/day) | No. of animals | Route of administration | Measuring time point | Male | | Female | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | $C_{max}$ (ng/mL) | $AUC_{24h}$ (ng·h/mL) | $C_{max}$ (ng/mL) | $AUC_{24h}$ (ng·h/mL) |
| Mice | 13 weeks | 2 | 18[a)] | p.o. | Day 1 | 443 | 2315 | 508 | 2607 |
| | | | | | Week 13 | 350 | 2143 | 508 | 2418 |
| | | 4 | 18[a)] | | Day 1 | 982 | 4743 | 757 | 4993 |
| | | | | | Week 13 | 613 | 4069 | 748 | 4764 |
| | | 8 | 18[a)] | | Day 1 | 1305 | 10,721 | 1348 | 7865 |
| | | | | | Week 13 | 991 | 9608 | 1003 | 8988 |
| | | 16 | 18[a)] | | Day 1 | 2531 | 13,736 | 2310 | 17,415 |
| | | | | | Week 13 | 1782 | 15,960 | 1725 | 14,895 |
| | 13 weeks | 100 | 18[a)] | p.o. | Day 1 | 4981 | 27,604 | 3865 | 35,368 |
| | | | | | Week 13 | 2925 | 24,318 | 2967 | 25,478 |
| | | 300 | 18[a)] | | Day 1 | 5542 | 58,967 | 8436 | 87,410 |
| | | | | | Week 13 | 4078 | 52,419 | 4318 | 54,890 |
| | | 1000 | 18[a)] | | Day 1 | 8027 | 101,553 | 17,213 | 158,833 |
| | | | | | Week 13 | 5196 | 80,724 | 6,42 | 87,828 |
| | 6 months | 10 | 38[a)] | p.o. | Day 22 | 869 | 4876 | 1408 | 5703 |
| | | | | | Day 177 | 826 | 5614 | 902 | 5842 |
| | | 100 | 38[a)] | | Day 22 | 2757 | 38,528 | 2920 | 34,929 |
| | | | | | Day 177 | 2381 | 21,289 | 2101 | 32,491 |
| | | 1000 | 38[a)] | | Day 22 | 5494 | 88,893 | 6377 | 108,687 |
| | | | | | Day 177 | 4640 | 72,183 | 5874 | 76,010 |
| Rats | 13 weeks | 30 (male)<br>0.3 (female) | 6 | p.o. | Day 1 | 214 | 1665 | 96.4 | 1389 |
| | | | | | Day 88 | 169 | 1281 | 76.5 | 592 |
| | | 100 (male)<br>3 (female) | 6 | | Day 1 | 332 | 2519 | 814 | 5754 |
| | | | | | Day 88 | - | - | 1002 | 6984 |
| | | 300 (male)<br>10 (female) | 6 | | Day 1 | 349 | 3880 | 1791 | 18,552 |
| | | | | | Day 88 | - | - | - | - |
| | | 1000 (male)<br>30 (female) | 6 | | Day 1 | 659 | 7831 | 2725 | 44,015 |
| | | | | | Day 88 | - | - | - | - |
| Monkeys | 13 weeks | 25 | 3 | p.o. | Day 1 | 1441 | 12,136 | 1744 | 21,098 |
| | | | | | Week 13 | 1842 | 13,254 | 1728 | 12,461 |
| | | 85 | 3 | | Day 1 | 1523 | 12,372 | 1288 | 15,352 |
| | | | | | Week 13 | 1638 | 12,592 | 2084 | 20,293 |
| | | 300 | 3 | | Day 1 | 1098 | 14,747 | 2139 | 22,711 |
| | | | | | Week 13 | 3102 | 32,523 | 2821 | 23,307 |
| | 12 months | 60 | 3 | p.o. | Day 1 | 774 | 9964 | 1159 | 12,996 |
| | | | | | Day 101 | 1213 | 9983 | 1509 | 10,718 |
| | | | | | Day 358 | 1265 | 16,443 | 1596 | 17,526 |
| | | 180 | 3 | | Day 1 | 1613 | 19,537 | 1653 | 22,401 |
| | | | | | Day 101 | 1528 | 14,141 | 1371 | 12,724 |
| | | | | | Day 358 | 2413 | 23,841 | 1833 | 22,561 |
| | | 600 | 3 | | Day 1 | 2158 | 34,717 | 1622[b)] | 25,678[b)] |
| | | | | | Day 101 | 2554 | 23,548 | 2757 | 23,451 |
| | | | | | Day 358 | 4533 | 42,608 | 2367 | 26,936 |

Mean; -, No surviving animals, precluding measurement
a) n = 3/measuring time point
b) n = 2

## 4.2 Distribution

### 4.2.1 Tissue distribution (CTD 4.2.2.2.1)

Following a single oral administration of $^{14}$C-apremilast (500 mg/kg) to male and female albino mice (n = 30) or pigmented male mice (n = 5), tissue distribution was investigated by quantitative whole-body autoradiography.

In albino mice, the radioactivity was distributed throughout the whole body within 2 hours after administration, showing particularly high concentrations in the liver, kidneys, and pancreas. At 72 hours after administration, the radioactivity concentration decreased below the lower limit of quantitation (0.71 μg eq./g) in all tissues except liver, skin, uvea, nasal mucosa, and gastrointestinal mucosa and, at 168 hours after administration, the radioactivity concentration was below the lower limit of quantitation in all tissues. No clear sex difference was observed in the tissue distribution of the radioactivity.

In pigmented mice, radioactivity was distributed throughout the whole body as was observed in albino mice, and was detected in most of the tissues even at 72 hours after administration but, at 168 hours

after administration, the radioactivity concentration was below the lower limit of quantitation (0.81 μg eq./g) in all tissues.

### 4.2.2 Plasma protein binding (CTD 4.2.2.3.1)

The protein binding of apremilast (0.25-2.5 μg/mL) in plasma was 88.6% in mice, 90.6% in rats, 80.9% in rabbits, 84.3% in monkeys, and 68.3% in humans, showing no difference regardless of apremilast concentration.

### 4.2.3 Fetal transfer and placental transfer (CTD 4.2.3.5.1.3 and 4.2.3.5.2.7)

Apremilast (10, 20, 40, 80 mg/kg) was orally administered to female mice (n = 3/group) from before pregnancy up to Gestation Day 15. At 24 hours after the last dose, plasma apremilast concentration in fetuses was below the lower limit of quantitation in 6 of 10 fetuses available for plasma apremilast concentration measurement (2 in the 10 mg/kg group, 2 in the 20 mg/kg group, 1 in the 40 mg/kg group, 1 in the 80 mg/kg group). In fetuses that contained quantifiable level of apremilast, plasma apremilast concentration was 7.19 ng/mL in the 10 mg/kg group, 108 ng/mL in the 20 mg/kg group, and 943 ng/mL in the 80 mg/kg group. The ratio of the mean plasma apremilast concentration in fetuses to that in maternal animals was 0.81 to 1.07.

Apremilast (20, 50, 200, 1000 mg/kg) was orally administered to pregnant monkeys (n = 16/group) from Gestation Day 20 to 50, followed by a single-dose administration of apremilast on Gestation Day 100. At 5 hours after administration, plasma apremilast concentration in fetuses was 176 ng/mL in the 20 mg/kg group, 253 ng/mL in the 50 mg/kg group, 165 ng/mL in the 200 mg/kg group, and 130 ng/mL in the 1000 mg/kg group. The ratio of the mean plasma apremilast concentration in fetuses to that in maternal animals was 0.3 to 0.4.

The above results suggested that apremilast crosses the placenta.

## 4.3 Metabolism

### 4.3.1 *In vitro* studies

#### 4.3.1.1 Studies with liver microsomes (CTD 4.2.2.4.3)

Liver microsomes isolated from male and female mice, rats, rabbits, dogs, monkeys, and humans were incubated with $^{14}$C-apremilast (1-50 μmol/L) in the presence of beta-nicotinamide adenine dinucleotide phosphate (β-NADPH). As a result, unchanged apremilast and M1/M2 were detected in all animal species. Other metabolites detected were M3, M5, and M7 in mice, M3 in rats (male only), M3, M4, M7, M8 (male only), M9, and M10 in rabbits, M3 and M7 in dogs, M3 and M5 in monkeys, and M3 and M7 in humans. After incubation in the absence of β-NADPH, the following metabolites were not detected: M3 and M5 in mice and monkeys, M3 in male rats, dogs, and humans, and M3, M4, M8, M9, and M10 in rabbits, which suggested that cytochrome P450 is involved in the production of these metabolites. M1/M2 was detected in a similar amount after incubation in phosphate buffer (pH 7.4), suggesting that the amide linkage of the phthalimide constituting the chemical structure of apremilast is hydrolyzed non-enzymatically.

#### 4.3.1.2 Studies with hepatocytes (CTD 4.2.2.4.2)

Hepatocytes isolated from mice, rats, rabbits, dogs, monkeys, and humans were incubated with $^{14}$C-apremilast (5, 25 μmol/L) in the presence of β-NADPH. Unchanged apremilast, M1/M2, M3, M7, M12, M14, M18, and M23 were detected in all animal species. Other metabolites detected were M4 and M11 in mice, rats, and rabbits, M15 in rats, rabbits, and monkeys, and M16 and M17 in mice, rats, and humans. M1/M2 and M18 were detected in a similar amount after apremilast was incubated with the medium not containing hepatocytes.

#### 4.3.1.3 Effect of age (CTD 4.2.2.4.4)

Using liver microsomes derived from mature and juvenile (14 days old) mice, liver microsomes derived from human adults and children (6-11 years old), and hepatocytes derived from human adults and children (6-14 years old), the effect of age on the metabolism of apremilast was investigated. After human-derived samples were incubated with $^{14}$C-apremilast (10 μmol/L) in the presence of β-NADPH, unchanged apremilast, M1/M2, M3, M7 (liver microsomes only), M11, M12, M13, M14, M15, M17, and M18 were detected. The metabolites detected were not different according to age. In the liver

microsomes derived from mouse liver, unchanged apremilast, M1/M2, M11, M12, and M18 were detected. M7 was detected only in mature mice, and M13 and M14 only in juvenile mice. Each of the metabolites accounted for 0.8% of the total radioactivity.

#### 4.3.1.4 Study on CYP isoforms involved in the metabolism of apremilast (CTD 4.2.2.6.1)

After human liver microsomes were incubated with $^{14}$C-apremilast in the presence of β-NADPH, M1, M2, M3, and M5 were detected, whereas in the absence of β-NADPH, mainly M1 and M2 were detected, which suggested that M3 and M5 were produced by cytochrome P450-mediated metabolism.

Microsomes derived from insect cells expressing various human Cytochrome P450 (CYP) isoforms were incubated with $^{14}$C-apremilast (200 μmol/L) in the presence of heat-treated rat liver microsomal protein.[2)] As a result, M3 was produced only in the CYP3A4-expressing system. M5 was produced in each of CYP1A2-, CYP2A6-, CYP2C8-, CYP2C19-, CYP2E1-, and CYP3A4-expressing systems, but most abundantly in the CYP3A4-expressing system.

Human liver microsomes were incubated with $^{14}$C-apremilast (200 μmol/L) in the presence of β-NADPH and a selective inhibitor of each CYP isoform, and the effect on apremilast metabolism to M3 and M5 was investigated. Results are shown in Table 8, which suggest that apremilast is metabolized not only by CYP3A4 but also by other CYP isoforms. Although the investigation on metabolite M5 was performed in this study, the applicant determined that M5 is not a major metabolite in humans because no M5 was generated in the mass balance study in humans [see "4.3.2 *In vivo* studies"].

**Table 8. Effect of inhibitors of CYP isoforms on the production of apremilast metabolites M3 and M5**

| Inhibitor | Concentration (μmol/L) | Inhibition of M3 production (mean %) | Inhibition of M5 production (mean %) |
|---|---|---|---|
| Furafylline (inhibitor of CYP1A2) | 50 | 56.2 | 55.8 |
| 8-Methoxypsoralen (inhibitor of CYP2A6) | 10 | 58.7 | 71.5 |
| Sulfaphenazole (inhibitor of CYP2C8/9) | 20 | 30.6 | 0 |
| Tranylcypromine (inhibitor of CYP2C19) | 20 | 19.2 | 7.3 |
| Quinidine (inhibitor of CYP2D6) | 3 | 0 | 0 |
| Anti-CYP2E1 monoclonal antibody | -[a)] | 0 | 18.5 |
| Ketoconazole (inhibitor of CYP3A4) | 2 | 57.8 | 104.1 |

a) One-tenth of the total protein

### 4.3.2 *In vivo* studies (CTD 4.2.2.2.1, 4.2.2.2.3, 4.2.2.2.8, 4.2.2.4.1, and 5.3.3.1.2)

Following an intravenous administration of $^{14}$C-apremilast (10 mg/kg) to male and female mice, unchanged apremilast, M1/M2 and M15 were detected in plasma after 45 minutes and, within 24 hours after administration, unchanged apremilast, M1/M2, M12, and M15 were detected in urine, and unchanged apremilast, M1/M2, M3, M5, M9, M19, and M22 in feces. The metabolites detected were similar between males and females. Similar metabolites were detected following an oral administration of $^{14}$C-apremilast (500 mg/kg).

Following an intravenous administration of $^{14}$C-apremilast (5 mg/kg) to bile duct-cannulated male mice, unchanged apremilast, M7, M12, M13, M14, M16, M17, and M18 were detected in plasma after 1 hour and, within 48 hours after administration, unchanged apremilast, M3, M11, M17, M18, M21, and M23 were detected in bile, urine, and feces, M12, M13, M14, M15, and M16 in bile and urine, and M7 in bile and feces. Similar metabolites were detected following an oral administration of $^{14}$C-apremilast (10 mg/kg).

Following a single oral administration of $^{14}$C-apremilast (10 mg/kg) to male rats, M2, M3, M9, and M12 were detected in plasma after 12 hours and, within 24 hours after administration, M2, M3, M9, and M12 were detected in urine, and unchanged apremilast, M1, M2, M3, M5, M7, M8, and M9 in feces. Following a single oral administration of $^{14}$C-apremilast (10 mg/kg) to female rats, unchanged apremilast, M1, M2, and M12 were detected in plasma after 12 hours and, within 24 hours after administration, unchanged apremilast, M1, M2, M9, and M12 were detected in urine, and unchanged

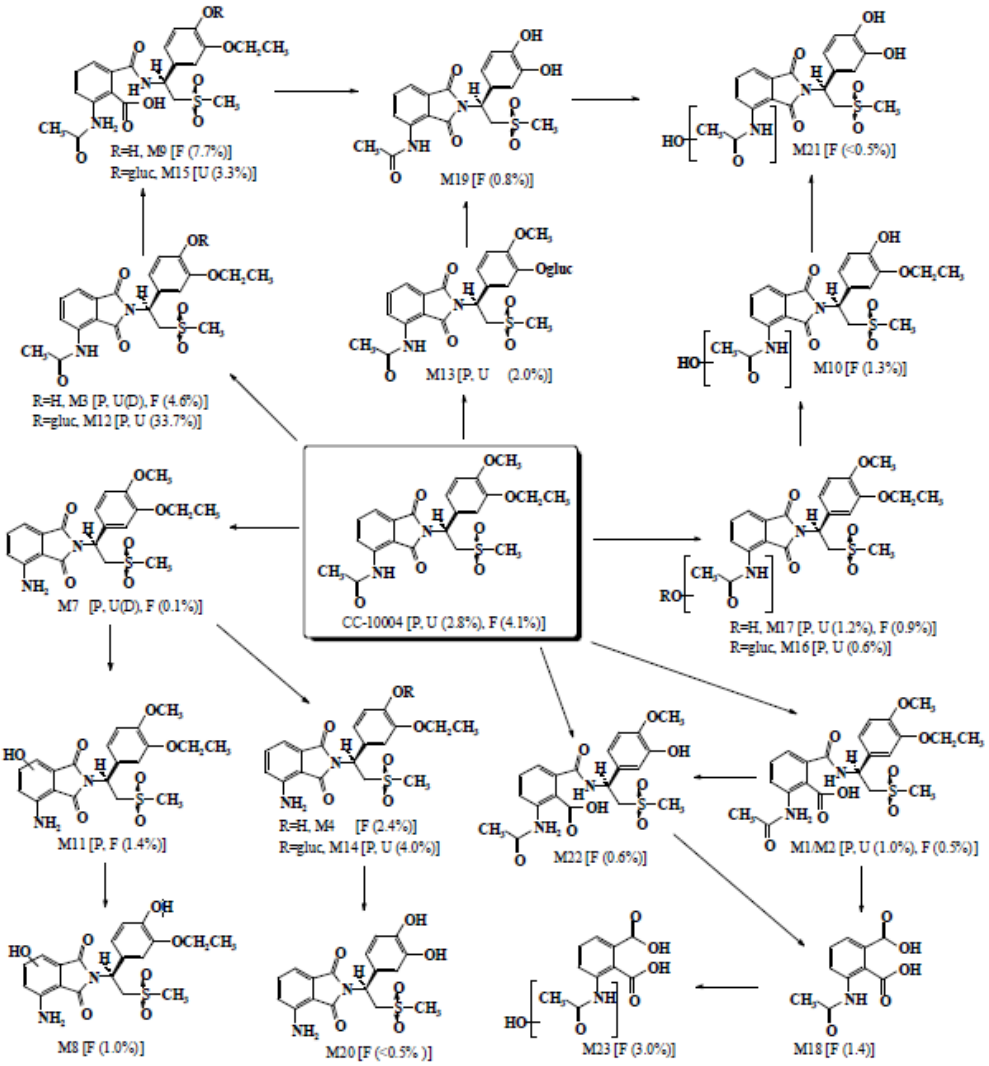
2) The heat-treated rat liver microsomal protein had no metabolic activity; it was used to assist the dissolution of compounds.

apremilast, M1, M2, M3, M5, M7, M8, and M9 were detected in feces. After repeat-dose administration, only M1 was detected in plasma of male rats at 12 hours after administration and unchanged apremilast, M1, M2, and M5 in plasma of female rats. Metabolites detected in urine and feces were similar to those detected after single-dose administration.

Following an intravenous administration of $^{14}$C-apremilast (1 mg/kg) to male and female monkeys, unchanged apremilast, M1/M2, M12, and M15 were detected in plasma after 2 hours and, within 72 hours after administration, M1/M2, M3, M9, M12, M13, and M15 were detected in urine, and, within 96 hours after administration, unchanged apremilast, M3, M4, M9, M10, and M19 in feces. The metabolites detected were similar between males and females. Similar metabolites were detected following an oral administration of $^{14}$C-apremilast (10 mg/kg).

After $^{14}$C-apremilast containing 100 μCi radioactivity was administered to male humans, unchanged apremilast, M7, M11, M12, M13, M14, and M16 were detected in plasma, and their $AUC_t$ was 2455, incalculable, 139, 2124, 133, 269, and 363 ng Eq·h/mL, respectively. Unchanged apremilast, M1/M2, M12, M13, M14, M15, M16, and M17 were detected in urine within 48 hours after administration, and unchanged apremilast, M1/M2, M3, M4, M7, M8, M9, M11, M12, M15, M16, M17, M18, M19, M20/M21, M22, and M23 were detected in feces within 96 hours after administration.

Based on the above metabolic studies, the metabolic pathways of apremilast were postulated as shown in Figure 2.




P, Metabolites detected in plasma; F, Metabolites detected in feces and recovery (%); U, Metabolites detected in urine and recovery (%), D, Detected but non-quantifiable.

**Figure 2. Possible metabolic pathways of apremilast in humans**

## 4.4 Excretion

### 4.4.1 Excretion in animals and in humans (CTD 4.2.2.2.1, 4.2.2.2.3, 4.2.2.2.8, 4.2.2.5.1, and 5.3.3.1.2)

Table 9 shows the excretion rates of radioactivity following the administration of $^{14}$C-apremilast to mice, rats, monkeys, and humans. The radioactivity was excreted mainly in feces in mice, rats, and monkeys. It was considered that, in mice, $^{14}$C-apremilast was excreted in feces mainly via bile.

**Table 9. Excretion rate of radioactivity following the administration of $^{14}$C-apremilast**

| Animal species | Route of administration | Dose (mg/kg) | Sampling time | Sex (No. of animals) | Mean percentage relative to radioactivity administered | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Urine | Bile | Feces | Total[a)] |
| Mice | i.v. | 10 | 168 hours | Male (14) | 7.8 | - | 66.2 | 90.6 |
| | | | | Female (15) | 8.7 | - | 71.3 | 91.1 |
| | p.o. | 500 | | Male (15) | 4.1 | - | 71.5 | 97.7 |
| | | | | Female (15) | 3.0 | - | 73.1 | 92.8 |
| Bile duct-cannulated mice | i.v. | 5 | 48 hours | Male (4) | 17.8 | 59.1 | 10.5 | 90.2 |
| | p.o. | 10 | | Male (4) | 15.1 | 53.9 | 15.6 | 91.0 |
| Rats | p.o. | 10[b)] | 24 hours | Male (3) | 15.7 | - | 57.9 | 74.5 |
| | | | | Female (3) | 29.6 | - | 28.2 | 52.6 |
| Monkeys | i.v. | 1 | 168 hours | Male (3) | 15.7 | - | 56.6 | 79.6 |
| | | | | Female (3) | 16.2 | - | 56.0 | 81.1 |
| | p.o. | 10 | | Male (3) | 17.2 | - | 69.3 | 93.5 |
| | | | | Female (3) | 20.3 | - | 68.2 | 95.8 |
| Humans | p.o. | 20[c)] | 216 hours | Male (6) | 57.9 | - | 39.2 | 97.1 |

i.v., Intravenous administration; p.o., Oral administration; -, Not calculated

a) Total recovery including radioactivity in cage washes and animal sheddings

b) A single dose of $^{14}$C-apremilast was administered after a 6-day repeated administration of apremilast

c) Unit, mg

### 4.4.2 Excretion in milk (CTD 4.2.2.5.2)

Following a single oral administration of apremilast (10 mg/kg) to female mice (n = 5) on Postpartum Day 13, apremilast concentrations in plasma and in milk were 984 and 1441 ng/mL, respectively, at 1 hour after administration and 138 and 186 ng/mL, respectively, at 6 hours after administration, suggesting that apremilast was excreted in milk.

## 4.5 Pharmacokinetic drug interactions

### 4.5.1 Enzyme inhibition and enzyme induction (CTD 4.2.2.6.2 to 4.2.2.6.4)

Using human liver microsomes, the inhibitory effect of apremilast (1-100 μmol/L) against the metabolic activities of various CYP isoforms was investigated in the presence of each of their substrates and enzymes. Apremilast did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in a concentration-dependent manner, but weakly inhibited CYP2C8 with $IC_{50}$ of 56.1 μmol/L.

Using primary cultured human liver cells, the effect of once daily treatment with apremilast (1, 10, 100 μmol/L) for 3 days on the metabolic activities of various CYP isoforms was investigated in the presence of each of their substrates. Treatment with apremilast (1, 10, 100 μmol/L) caused a 10% increase, 33% decrease, and 43% decrease, respectively, in CYP1A2 activity, 6% increase, 35% decrease, and 73% decrease in CYP2C9 activity, and 20% increase, 44% increase, and 372% increase in CYP3A4 activity. Apremilast had no effect on CYP2B6 and CYP2C19 activities. Thus, treatment with apremilast decreased CYP1A2 and CYP2C9 activities and increased CYP3A4 activity. Apremilast concentrations 10 and 100 μmol/L were approximately 14 and 140 times $C_{max}$ (334 ng/mL) following twice daily multiple dosing of 30 mg apremilast to Japanese patients with psoriasis.

### 4.5.2 Transporters (CTD 4.2.2.6.5 to 4.2.2.6.9)

Using a porcine kidney epithelial cell line expressing human P-glycoprotein (P-gp), the activity of apremilast to serve as a substrate or an inhibitor of P-gp was investigated. The efflux ratio (apparent permeability [$P_{app}$] B→A/$P_{app}$ A→B) of apremilast (10 μmol/L) in the control porcine kidney epithelial cell line was 1.1. In contrast, the efflux ratio ($P_{app}$ B→A/$P_{app}$ A→B) of apremilast (10 μmol/L) in the

human P-gp-expressing porcine kidney epithelial cell line was 19, and apremilast transport was inhibited by 92% in the presence of ketoconazole (30 μmol/L), a P-gp inhibitor, suggesting that apremilast is a substrate for P-gp. When the human P-gp-expressing porcine kidney epithelial cell line was treated with apremilast (0.01-50 μmol/L), apremilast up to 20 μmol/L did not affect the transport of digoxin, a substrate of P-gp, but, at 50 μmol/L, inhibited the transport by 31%, suggesting that apremilast at ≥50 μmol/L inhibits P-gp-mediated transport.

*Xenopus laevis* oocytes expressing human organic anion transporter (OAT) 1 or OAT3 was treated with apremilast (2, 10 μmol/L). Apremilast had no effect on the uptake of a substrate for OAT3, while apremilast at 10 μmol/L inhibited the uptake of an OAT1 substrate by 21%.

Membrane vesicles derived from cells expressing human breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP) 1, MRP2, MRP3, MRP4, or MRP8 were treated with apremilast (2, 20 μmol/L). Uptake of an MRP3 substrate was inhibited by 22.8% and 21.8%, respectively, and uptake of an MRP8 substrate by 42.7% and 59.8%, respectively, whereas the uptake of BCRP, MRP1, MRP2, and MRP4 substrates was not affected. The applicant explained that the role of MRP8 is unclear, precluding the assessment of the clinical effect of MRP8 inhibition.

Human fetal kidney 293 cell line expressing human organic cation transporter (OCT) 2, organic anion transporting polypeptide (OATP) 1B1, or OATP1B3 was treated with apremilast (2, 20 μmol/L). Treatment with 20 μmol/L apremilast inhibited the uptake of an OATP1B1 substrate by 26.1%, but did not affect the uptake of an OCT2 or OATP1B3 substrate.

When a human BCRP-expressing porcine kidney epithelial cell line was treated with apremilast (1, 10 μmol/L), the efflux ratio ($P_{app}$ B→A/$P_{app}$ A→B) was 1.4 and 1.1, respectively, and the ratio was not changed by treatment with an inhibitor of BCRP, suggesting that apremilast is not a substrate of BCRP.

Human OAT1- or OAT3-expressing $S_2$ cells and human OCT2-, OATP1B1-, or OATP1B3-expressing human fetal kidney 293 cell line was treated with apremilast (1, 10 μmol/L). The extent of the intracellular uptake of apremilast was similar to that observed when non-expressing cells were treated with apremilast, and not changed by the inhibitor of each transporter. These results suggested that apremilast is not a substrate of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.

### 4.R Outline of the review conducted by PMDA

Based on the submitted data of nonclinical pharmacokinetic studies, PMDA concluded that the behavior of apremilast in the body has been elucidated to a sufficient extent, although the binding rate of apremilast to human plasma proteins was low.

## 5. Toxicity and Outline of the Review Conducted by PMDA

**Summary of the submitted data**

The applicant submitted the results from the toxicology studies, namely single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (e.g., immunotoxicity studies, studies on the mechanism of toxicity, phototoxicity studies).

Unless specified otherwise, 1% carboxymethylcellulose solution was used as vehicle in *in vivo* studies and, in oral administration, apremilast was administered by oral gavage.

### 5.1 Single-dose toxicity

#### 5.1.1 Single oral dose toxicity study in mice (CTD 4.2.3.1.1)

A single dose of apremilast (2000 mg/kg) was administered orally to mice (n = 5/sex). No death occurred. The clinical finding observed was lid closure. Based on the above, the approximate lethal dose was determined to be >2000 mg/kg.

#### 5.1.2 Single intravenous dose toxicity study in mice (CTD 4.2.3.1.2)

A single dose of apremilast (120 mg/kg [vehicle, Intralipid 20 solution containing 8% DMSO]) was administered intravenously to mice (n = 5/sex). Death occurred in males. Findings observed in surviving

animals were respiratory distress and lid closure. In the preliminary study for dose finding, apremilast (50, 70, 100, 150, 200 mg/kg) was administered intravenously to 1 each of male and female. Death occurred in the male in the 150 mg/kg group and in both the male and female in the 200 mg/kg group. Based on the above, the approximate lethal dose was determined to be >120 mg/kg in males and >200 mg/kg in females.

### 5.1.3 Single oral dose toxicity study in rats (CTD 4.2.3.1.3)

A single dose of apremilast (2000 mg/kg in males, 300 mg/kg in females) was administered orally to rats (n = 5/sex). Death occurred in males. Findings observed in surviving animals included diarrhea, lid closure, lethargy, hunchback position, chromodacryorrhea, dyspnoea, respiratory distress, abnormal breath sounds, debility, piloerection, unkempt fur, and decreased body weight. In the preliminary study for dose finding, a single dose of apremilast was administered orally to males (n = 1 or 2/group) at the dose of 1000, 1500, or 2000 mg/kg and to females (n = 2 or 3/group) at the dose of 200, 400, 700, 1000, 1500, or 2000 mg/kg. Death occurred in females in the ≥400 mg/kg groups. Based on the above, the approximate lethal dose was determined to be >2000 mg/kg in males and >300 mg/kg in females.

### 5.1.4 Single intravenous dose toxicity study in rats (CTD 4.2.3.1.4)

A single dose of apremilast (60 mg/kg [vehicle, Intralipid 20 solution containing 8% DMSO]) was administered intravenously to rats (n = 5/sex). No death occurred. Findings observed included respiratory distress, lethargy, lacrimation, lid closure, piloerection, unkempt fur, and decreased body weight. In the preliminary study for dose finding, a single dose of apremilast (50, 60, 75, 100 mg/kg) was administered intravenously to rats (n = 1 or 2/sex/group). Death occurred in females in the ≥75 mg/kg groups. Based on the above, the approximate lethal dose was determined to be >60 mg/kg and <75 mg/kg in females.

### 5.1.5 Single oral dose toxicity in monkeys (CTD 4.2.3.2.9)

In the 14-week repeated oral dose toxicity study in monkeys, no death occurred after the initial dose of apremilast (1000 mg/kg) and no apremilast-related findings were observed. Based on the above, the approximate lethal dose was determined to be >1000 mg/kg.

## 5.2 Repeat-dose toxicity

Repeat-dose toxicity studies were conducted in mice, rats, and monkeys as repeated oral administration studies. Main toxic findings observed in mice and rats included vasculitis, infiltration of inflammatory cells into the perivascular area of the lung, inflammation or bleeding of liver, gallbladder, mesenterium, pancreas, and mammary gland, hyperkeratosis of the esophagus and anterior stomach, decreased lymphocyte count, and depletion of lymphoid cells in lymphoid tissues. In monkeys, decreased lymphocyte count, etc., was observed. AUC in the 6-month oral administration study in mice at the no observed adverse effect level (NOAEL) (10 mg/kg/day) and in the 12-month oral administration study in monkeys at the NOAEL (600 mg/kg/day) was 1.1 and 6.6 times, respectively, the estimated AUC in Japanese patients with psoriasis in twice daily multiple dosing of apremilast (30 mg).

### 5.2.1 Twenty-eight-day repeated oral dose toxicity study in mice (CTD 4.2.3.2.2)

Apremilast (0 [vehicle], 250, 600, 1500 mg/kg/day) was administered orally for 4 weeks to mice (n = 12/sex/group). One female in the 600 mg/kg/day group died of unknown cause and 2 females in the 1500 mg/kg/day group showed systemic arteritis, resulting in death in one and moribund sacrifice in the other. Findings observed in the surviving animals were, in males and females in the ≥250 mg/kg/day groups, increased neutrophil count, increases in globulin and total protein, decreased albumin/globulin ratio, increased splenic weight, aortitis, synovitis, centrilobular hepatocellular hypertrophy, infiltration of inflammatory cells into perivascular area of the lung, increased haematopoiesis in liver, submandibular lymph nodes, mesenteric lymph nodes, bone marrow, and spleen, hyperkeratosis in anterior stomach, gastric hypertrophy (males), and splenic swelling (females); in the ≥600 mg/kg/day groups, arteritis in thymus in males and abdominal distension, hunchback position, emaciation, and gastric hypertrophy in females; and in the 1500 mg/kg/day group, increased liver weight, enlargement of the liver, and gastritis in both males and females, reduced body weight gain in males, and increased white blood cell count and arteritis of thymus in females. Based on the above, the NOAEL was determined to be <250 mg/kg/day.

### 5.2.2 Four-week repeated oral dose toxicity study in mice (CTD 4.2.3.2.3)

Apremilast (0 [vehicle], 5, 25, 75, 150 mg/kg/day) was administered orally for 4 weeks to mice (n = 12/sex/group). Findings observed in surviving animals were, in males in the ≥5 mg/kg/day groups, arteritis at the aortic root; in males in the ≥25 mg/kg/day groups, decreased lymphocyte count and arteritis in thymus; in the ≥75 mg/kg/day groups, hyperkeratosis in anterior stomach in males and females, infiltration of inflammatory cells into the perivascular area of the lung in males, and decreased lymphocyte count in females; and in the ≥150 mg/kg/day groups, arteritis in kidney in males, and decreased albumin, increased globulin, decreased albumin/globulin ratio, arteritis at the aortic root, and gastric hypertrophy in females. Thus, with the vascular and perivascular inflammation and hyperkeratosis in anterior stomach detected by histopathological examination as the indices, the NOAEL was determined to be <5 mg/kg/day in males and 25 mg/kg/day in females.

### 5.2.3 Four-week repeated oral dose toxicity study in mice (CTD 4.2.3.2.4)

Apremilast (0 [vehicle], 1, 2, 4 mg/kg/day) was administered orally for 4 weeks to mice (n = 12/sex/group). No apremilast-related death or toxic findings were observed, from which the NOAEL was determined to be 4 mg/kg/day.

### 5.2.4 Thirteen-week repeated oral dose toxicity study in mice (CTD 4.2.3.2.5)

Apremilast (0 [vehicle], 2, 4, 8, 16 mg/kg/day) was administered orally for 13 weeks to mice (n = 12/sex/group). Males and females in the ≥16 mg/kg/day groups showed arteritis at the aortic root and females in the same groups showed infiltration of inflammatory cells into perivascular area of the lung and arteritis in thymus, from which the NOAEL was determined to be 8 mg/kg/day.

### 5.2.5 Ninety-day repeated oral dose toxicity study in mice (CTD 4.2.3.2.6)

Apremilast (0 [vehicle], 100, 300, 1000 mg/kg/day) was administered orally for 90 days to mice (n = 10/sex/group). Findings observed were, in the ≥100 mg/kg/day groups, increases in food consumption and body weight and increased thymic weight in males and females and increased liver weight in females; in the ≥300 mg/kg/day groups, increased neutrophil count, increased haptoglobin, decreased lymphocyte count, and effect on the lung (vascular or peribronchiolar inflammation, vascular degeneration, haemorrhage) in males and females, effect on the heart (degeneration or necrosis of cardiac muscles, fibrosis, mineral deposition, chronic inflammation, pigmentation), depletion of lymphoid cells in thymus, spleen, and mesenteric lymph nodes, and perivascular inflammation in mesenterium and pancreas in males, and arteritis at the aortic root in females; and in the 1000 mg/kg/day group, centrilobular hepatocellular hypertrophy in males and females and increased liver weight in males. Thus, with the inflammatory reactions manifest as increased neutrophil count or increased haptoglobin and histopathological findings of heart, lung, etc., as the indices, the NOAEL was determined to be 100 mg/kg/day.

### 5.2.6 Six-month repeated oral dose toxicity study in mice (CTD 4.2.3.2.7)

Apremilast (0 [vehicle], 10, 100, 1000 mg/kg/day) was administered orally for 6 months to mice (n = 15/sex/group). Death occurred in 1 male in the 100 mg/kg/day group and 2 males and 1 female in the 1000 mg/kg/day group. The dead animals showed vascular and perivascular inflammation and necrosis, haemorrhagic foci in skeletal muscles, abdominal wall, mesenterium, mammary gland, muscular tissues, etc., and hepatic infarction. Findings observed in the surviving animals were, in the ≥10 mg/kg/day groups, increased total protein in males and increased body weight gain in females; in the ≥100 mg/kg/day groups, increased neutrophil count, increased haptoglobin, increased liver weight, effect on the heart (inflammation at the aortic root, inflammation of cardiac muscles, perivascular inflammation, cartilaginous metaplasia at the aortic root, mineral deposit in blood vessels), and centrilobular hepatocellular hypertrophy in the liver in males and females, decreased white blood cell count, increased testicular weight, vascular and perivascular inflammation in the liver, and pericholangial fibrosis in males, and increases in food consumption and body weight gain, increased globulin, and decreased brain weight in females; and in the 1000 mg/kg/day group, decreased albumin/globulin ratio and infiltration of mononuclear cells in pancreas in males and females; increased globulin in males, and increased heart weight, pericholangial fibrosis, gallbladder inflammation and necrosis, and vascular and perivascular inflammation in the mesenterium in females. Thus, with death, inflammatory reactions manifest as increased neutrophil count or increased haptoglobin and histopathological findings of heart, liver, pancreas, gallbladder, etc., as the indices, the NOAEL was determined to be 10 mg/kg/day.

### 5.2.7 Ninety-day repeated oral dose toxicity study in rats (CTD 4.2.3.2.8)

The initial plan had been to orally administer apremilast for 92 days to male rats (n = 10/group) at the dose of 0 (vehicle), 30, 100, 300, or 1000 mg/kg/day and to female rats (n = 10/group) at the dose of 0 (vehicle), 0.3, 3, 10, or 30 mg/kg/day. However, because of the clear signs of toxicity, administration was discontinued at 48, 11, and 9 days after the start of administration in males in the 100, 300, and 1000 mg/kg/day groups, and at 26 and 9 days after the start of administration in females in the 10 and 30 mg/kg/day groups. Death or moribund sacrifice occurred in 1 male in the 30 mg/kg/day group, 10 males in the 100 mg/kg/day group, 10 males in the 300 mg/kg/day group, 7 males in the 1000 mg/kg/day group, 10 females in the 10 mg/kg/day group, and 6 females in the 30 mg/kg/day group. The dead animals showed lipoatrophy in the mesenterium, vascular degeneration, haemorrhage, perivascular fibrosis and inflammation, haemorrhage and inflammation at the aortic root of the heart, perivascular and epicardial inflammation, effect on the stomach and intestinal tract (mucosal inflammation, haemorrhage, congestion, erosion, or ulcer), depletion or necrosis of lymphoid cells in lymphoid tissues including lymph nodes, spleen, thymus, etc., neutrophilic inflammation, adrenocortical hypertrophy or hyperplasia, haemorrhage, atrophy or excessive mucus production in acinar cells of the salivary gland, and hyperkeratosis in the esophagus. Findings observed in the surviving animals were decreases in body weight and food consumption, increases in white blood cell count and neutrophil count, decreased albumin, increased globulin, decreased albumin/globulin ratio, increased haptoglobin, decreased thymic weight, depletion of lymphoid cells in lymphoid tissues, etc., all of which were observed in both males and females of all treatment groups. Based on the above, the NOAEL was not determined.

### 5.2.8 Four-week repeated oral dose toxicity study in monkeys (CTD 4.2.3.2.11)

Apremilast (0 [vehicle], 50, 180, 650 mg/kg/day) was administered orally for 4 weeks to monkeys (n = 3/sex/group). Findings observed were, in males in the ≥50 mg/kg/day groups, salivation and increased neutrophil count; in the ≥180 mg/kg/day groups, vomiting in males and females, arteritis in males, and salivation in females; and in the 650 mg/kg/day group, increased liver weight in males and females and arteritis in females. Arteritis, which was observed in 1 male and 2 females, was minimal and localized, and no such findings were observed in 13-week and 12-month long-term toxicity studies, from which they were considered to be spontaneous occurrences. Any changes other than arteritis were not accompanied by associated histopathological changes, suggesting that they were findings of low toxicological significance. Based on the above, the NOAEL was determined to be 650 mg/kg/day.

### 5.2.9 Thirteen-week repeated oral dose toxicity study in monkeys (CTD 4.2.3.2.12)

Apremilast (0 [vehicle], 25, 85, 300 mg/kg/day) was administered orally for 13 weeks to monkeys (n = 3/sex/group). Findings observed were salivation in males and females in the ≥25 mg/kg/day groups and vomiting or dry vomiting in males and females in the 300 mg/kg/day group. None of these changes were accompanied by associated histopathological changes, suggesting that they were findings of low toxicological significance. Based on the above, the NOAEL was determined to be 300 mg/kg/day.

### 5.2.10 Twelve-month repeated oral dose toxicity study in monkeys (CTD 4.2.3.2.13)

Apremilast (0 [vehicle], 60, 180, 600 mg/kg/day) was administered orally for 12 months to monkeys (n = 5/sex/group). Findings observed were, in the ≥60 mg/kg/day groups, decreases in T cells and natural killer cells in males; in the ≥180 mg/kg/day groups, increases in fibrinogen and haptoglobin in males and females, and increased C-reactive protein in males; and in the 600 mg/kg/day group, increased neutrophil count in males and females. None of these changes were accompanied by associated histopathological changes, suggesting that they were findings of low toxicological significance. Based on the above, the NOAEL was determined to be 600 mg/kg/day.

## 5.3 Genotoxicity (CTD 4.2.3.3.1.1, 4.2.3.3.1.2, 4.2.3.3.2)

The following genotoxicity studies were conducted: A bacterial reverse mutation assay and a chromosomal aberration assay in cultured human peripheral lymphocytes as *in vitro* studies; and a micronucleus assay using mouse bone marrow cells as the *in vivo* study. All results of assays were negative, from which it was determined that apremilast was non-genotoxic.

### 5.4 Carcinogenicity

As carcinogenicity studies, 104-week oral dose carcinogenicity studies were conducted in mice and rats. Apremilast did not cause any increase in the occurrences of neoplastic lesions.

#### 5.4.1 A 104-week oral dose carcinogenicity study in mice (CTD 4.2.3.4.1.1)

Apremilast (0 [vehicle], 100, 300, 1000 mg/kg/day) was orally administered repeatedly to mice (n = 70/sex/group). In order to ensure the number of surviving animals, the treatment duration and dose were changed as follows: Apremilast was administered up to Week 103 and 99, respectively, in males and females in the 100 mg/kg/day group; up to Week 98 and 96, respectively, in males and females in the 300 mg/kg/day group with dose reduction to 200 mg/kg/day from Week 73 in both males and females; and up to Week 73 and 102, respectively, in males and females in the 1000 mg/kg/day group with dose reduction to 500 mg/kg/day from Week 73 in females. In males in the ≥100 mg/kg/day groups and in females in the ≥300 mg/kg/day groups, early death was caused by haemorrhage at skeletal muscles, which was likely attributable to inflammation and degenerative change of blood vessels. Males showed a tendency of dose-dependent decrease in the survival rate.

No apremilast-related neoplastic lesions were observed. The following non-neoplastic lesions were observed: Haemorrhage from skeletal muscles, skin, intraperitoneal soft tissues, bones, mammary gland, uterine cervix, and vagina, inflammation at the aortic root or in the blood vessels, epicardial and perivascular fibrosis, growth of subendocardial spindle cells, vascular wall hypertrophy, infiltration of lymphoid cells in the lung, and enhanced mucus production in the vaginal epithelia.

#### 5.4.2 A 104-week oral dose carcinogenicity study in rats (CTD 4.2.3.4.1.2)

Apremilast (0 [vehicle], 0.3 [females], 1 [females], 3 [males and females], 10 [males], 20 [males] mg/kg/day) was orally administered repeatedly to rats (n = 70/sex/group). In order to ensure the number of surviving animals, the treatment duration and dose were changed as follows: (1) In males, apremilast was administered up to Week 91 in the 3 mg/kg/day group, up to Week 89 in the 10 mg/kg/day group with dose reduction to 6 mg/kg/day from Week 66, and up to Week 66 in the 20 mg/kg/day group and (2) in females, apremilast was administered up to Week 103, 101, and 94, respectively, in the 0.3, 1, and 3 mg/kg/day groups. Early death occurred due to gastrointestinal inflammation or necrosis in males in the ≥3 mg/kg/day groups and in females in the 1 mg/kg/day group, with males showing a tendency of dose-dependent decrease in the survival rate.

No apremilast-related neoplastic lesions were observed. The following non-neoplastic lesions were observed: Inflammation, erosion, or ulcer of the gastrointestinal tract, goblet cell hyperplasia, acute inflammation of lymphoid tissues (e.g., thymus, submandibular lymph nodes, mesenteric lymph nodes) or lymphoid cell hyperplasia, myocardial muscle necrosis or fibroplasia, vasculitis in the liver, periosteal bone growth in the femur, and enhanced mucus production in the vaginal epithelia.

### 5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies were conducted: A study of fertility and early embryonic development to implantation in mice, studies of embryo-fetal development in mice, rabbits, and monkeys, a study for effects on pre- and postnatal development, including maternal function in mice, and a toxicity study in neonates.

As effects of apremilast on maternal animals, prolongation of days to successful copulation, decreased number of estrous cycles, and decreases in conception rate and pregnancy rate were observed in mice. Effects on embryos/fetuses were increased resorption number and increased rate of post-implantation loss, delayed ossification such as decreased number of ossified tarsal bones and incomplete ossification of supraoccipital bone in mice, and increased prenatal mortality (abortion) in monkeys. AUC of apremilast at the NOAEL for embryo-fetal development (10 mg/kg/day in mice, 20 mg/kg/day in monkeys) was 1.8 times (in mice) and 1.9 times (in monkeys) as that in Japanese patients with psoriasis receiving twice daily multiple dosing of apremilast (30 mg). Apremilast was excreted in milk [see “4.4.2 Excretion in milk”].

### 5.5.1 Fertility and early embryonic development to implantation in male and female mice (CTD 4.2.3.5.1.1)

Apremilast (0 [vehicle], 100, 300, 1000 mg/kg/day) was orally administered to male mice (n = 25/group) for approximately 8 weeks from 28 days before mating and to female mice (n = 25/group) from 15 days before mating until Gestation Day 7. Effects observed in males were increased testicular weight, decreases in fecundity rate and pregnancy rate in the ≥100 mg/kg/day groups, decreased testicular weight and prolongation in days to successful copulation in the ≥300 mg/kg/day groups, and increased body weight gain, increased heart weight, decreased prostate weight, and decreased number of animals with successful copulation in the 1000 mg/kg/day group. Effects observed in females were increased body weight gain during the premating period and gestation period, decreases in fertility and pregnancy rates, decreased number of surviving embryos, increased number of dead embryos, increased rate of postimplantation loss, and increased number of maternal animals with dead embryos in the ≥100 mg/kg/day groups, prolongation of days to successful copulation in the ≥300 mg/kg/day groups, and decreased number of animals with successful copulation in the 1000 mg/kg/day group. Based on the above, the NOAEL for fertility of males and females was determined to be <100 mg/kg/day.

### 5.5.2 Fertility and early embryonic development to implantation in male mice (CTD 4.2.3.5.1.2)

Apremilast (0 [vehicle], 1, 10, 25, 50 mg/kg/day) was administered orally to male mice (n = 18/group) from 70 days before mating for approximately 14 weeks including the period of mating with untreated female animals. Increased body weight gain was observed in the ≥10 mg/kg/day groups and increased testicular weight was observed in the ≥25 mg/kg/day groups. In contrast, no apremilast-related changes were noted in observations related to mating or fecundity or in sperm test parameters. Based on the above, the NOAEL for the fertility of males was determined to be 50 mg/kg/day.

### 5.5.3 Fertility and embryo-fetal development in female mice (CTD 4.2.3.5.1.3)

Apremilast (0 [vehicle], 10, 20, 40, 80 mg/kg/day) was administered orally to female mice (n = 18/group) from 15 days before mating until Gestation Day 15 including the period of mating with untreated male animals. Findings observed in maternal animals were increased body weight gain during the pre-mating period in the ≥10 mg/kg/day groups, increased heart weight, increased number of animals with anestrus period of ≥6 days, and increased days to successful copulation in the ≥20 mg/kg/day groups, and reduced body weight gain during the gestation period, decreased frequency of estrus, and increased number of maternal animals with total resorption of litter in the ≥40 mg/kg/day groups. Findings observed in fetuses were increased number of resorptions, increased rate of post-implantation loss, and decreased number of ossified tarsal bones of the hind limbs in the ≥20 mg/kg/day groups, and decreased fetal weight, decreased number of surviving fetuses, and incomplete ossification of supraoccipital bone in the ≥40 mg/kg/day groups. Based on the above, the NOAEL for the fertility of females, general toxicity of maternal animals, and fetal development was determined to be 10 mg/kg/day.

### 5.5.4 Embryo-fetal development in mice (CTD 4.2.3.5.2.5)

Apremilast (0 [vehicle], 250, 500, 750 mg/kg/day) was administered orally to pregnant mice (48 in the control group, 24 in each apremilast group) from Gestation Day 6 to Gestation Day 15. One animal in the 750 mg/kg/day group was moribund-sacrificed because of the aggravation of clinical signs. Effects observed in maternal animals were reduced body weight gain and decreased food consumption, decreased gravid uterus weight, and increases in number of early resorptions, late intra-uterine deaths, and increased rate of post-implantation losses in the ≥250 mg/kg/day groups, and increased number of maternal animals with total resorption of litter in the 750 mg/kg/day group. Effects observed in fetuses were decreased total litter weight, low fetal weight, and incomplete ossification of cranial bone, sternebrae, vertebrae, and lumbar vertebrae in the ≥250 mg/kg/day groups, and decreased placental weight in the ≥500 mg/kg/day groups. Based on the above, the NOAEL for embryos and fetuses was determined to be <250 mg/kg/day.

### 5.5.5 Embryo-fetal development in monkeys (CTD 4.2.3.5.2.7)

Apremilast (0 [vehicle], 20, 50, 200, 1000 mg/kg/day) was administered orally to pregnant monkeys (n = 16/group) from Gestation Day 20 to Gestation Day 50. Effects observed in maternal animals were salivation and vomiting in the ≥20 mg/kg/day groups, increased prenatal mortality (abortion) in the ≥50 mg/kg/day groups, and reduced body weight gain in the ≥200 mg/kg/day groups. No abnormalities were

observed in the external appearance, visceral organs, or skeletons of fetuses. Based on the above, the NOAEL for embryos and fetuses was determined to be 20 mg/kg/day.

### 5.5.6 Effects on pre- and postnatal development, including maternal function in mice (CTD 4.2.3.5.3.1)

Apremilast (0 [vehicle], 10, 80, 300 mg/kg/day) was administered orally to pregnant mice (n = 25/group) from Gestation Day 6 to Postpartum Day 20. Deaths for which a relationship to apremilast could not be ruled out occurred in the 300 mg/kg/day group. Effects observed in maternal animals were aggravations of clinical signs such as pale ears, hunchback position, dehydration, dyspnea, and hyperpnoea in the ≥80 mg/kg/day groups, and decreased body weight in the 300 mg/kg group. Effects observed in the offspring were increased number of total litter deaths, decreased births, decreased live births, decreased postnatal survival to Day 4, and decreased body weight in survival neonates up to Lactation Day 7 in the ≥80 mg/kg/day groups. It was suggested that the decreased body weight up to Lactation Day 7 was caused by the lack of nursing behavior of the maternal animals, as judged from the absence of milk in the stomach of the infants. Based on the above, the NOAEL for maternal animals and $F_1$ offspring was determined to be 10 mg/kg/day.

### 5.5.7 Thirteen-week repeated oral dose toxicity study in juvenile mice (CTD 4.2.3.5.4.2)

Apremilast (0 [vehicle], 1, 4, 10 mg/kg/day) was orally administered for 13 weeks to 7-day old mice (n = 30-39/sex/group), followed by a 10-week washout period in 16 to 20 animals in each group. Deaths for which a relationship to apremilast could not be ruled out occurred in females in the 10 mg/kg/day group. Males and females in the ≥4 mg/kg/day groups showed decreased body weight, and females in the ≥4 mg/kg/day groups showed dehydration and increases in lymphocyte count and B cell count, and males in the 10 mg/kg/day group showed dehydration and delayed prepuce separation. However, none of these changes were observed after the 10-week washout period. Based on the above, the NOAEL in juvenile mice was determined to be 10 mg/kg/day in males and 4 mg/kg/day in females.

## 5.6 Local tolerance

### 5.6.1 Skin irritation study in rabbits (CTD 4.2.3.6.1)

Hair on the female rabbits (n = 3) was removed and 0.5 mL of 0.3 mg/mL apremilast (vehicle, ethanol:propylene glycol = 2:3 [v/v%]) was applied, and application site was covered with an occlusive patch for 4 hours. No skin reactions such as erythema, crust formation, and swelling were observed up to 48 hours after the removal of the patch.

### 5.6.2 Skin sensitization study (CTD 4.2.3.6.2)

Using 3.0 mg/mL apremilast (vehicle, ethanol:propylene glycol = 2:3 [v/v%]), 0.4 mL of this solution was applied to the back of guinea pigs (n = 10/sex/group), and the application site was covered with an occlusive patch for 6 hours to sensitize the skin. The sensitization was performed once every week for 3 weeks and, at 2 weeks after the last sensitization, apremilast was applied to the skin to evaluate the skin-sensitizing effect of apremilast. No irritation reaction was observed up to 48 hours after apremilast application. When apremilast was applied again to the same animals, irritating changes were observed in 1 of 20 animals after 48 hours, from which it was concluded that apremilast is a weak sensitizer.

## 5.7 Other toxicity studies

### 5.7.1 Comparative toxicity study of oral administration of apremilast and CC-10007 (*R*-enantiomer) (CTD 4.2.3.7.7.1)

Vehicle, apremilast, or CC-10007 was administered orally to female rats (n = 15/group) at a dose of 50 mg/kg. Animals in the apremilast group showed aggravations of clinical signs such as decreases in body weight and food consumption, hunchback position, and emaciation, and all animals were moribund-sacrificed at 3 days after administration. In the CC-10007 group, no death occurred, but aggravations of clinical signs such as abdominal distension and pallor were observed during the administration period of up to 30 days.

### 5.7.2 Study of progression and reversibility of apremilast-associated inflammatory lesions (CTD 4.2.3.7.7.3)

Apremilast (300, 1000 mg/kg/day) was administered orally to female mice (n = 36/group) for 14 days, followed by a washout period of 31 or 76 days. In addition, apremilast (0 [vehicle], 1000 mg/kg/day)

was administered orally for 90 days to an extended treatment group. During the 14-day repeated administration period, animals in both the 300 and 1000 mg/kg/day groups showed increases in body weight and food consumption, increases in globulin and urea nitrogen, decreased albumin/globulin ratio, lymphocyte necrosis in thymus, depletion or inflammation of lymphocytes, hyperplasia of inflammatory lymphoid cells in the mesenteric lymph nodes, and hypertrophy of hepatocytes. All histological changes were reversible after the washout period of 31 or 76 days. Animals in the extended apremilast group showed, within 45 days after the start of treatment, lymphocyte necrosis in thymus, depletion or inflammation of lymphocytes, hyperplasia of inflammatory lymphoid cells in the mesenteric lymph nodes, hypertrophy of hepatocytes, etc., but these findings were not observed after Day 90 of administration. Thus, histological changes observed in the thymus, mesenteric lymph nodes, liver, etc., after apremilast administration to mice were reversible after the washout period of 31 or 76 days or after the 90-day repeated administration period.

### 5.7.3 Bacterial reverse mutation test for impurities of apremilast (CTD 4.2.3.7.7.5)

An *in silico* assessment of genotoxicity of RC6 and RC8, impurities of apremilast, using quantitative, structural activity relationship approaches showed that RC6 has an alert structure for mutagenicity. Therefore, a bacterial reverse mutation test was conducted on RC6 and the results were negative.

### 5.7.4 Phototoxicity study with mouse fibroblasts (CTD 4.2.3.7.7.4)

BALB/c 3T3 cells, a mouse fibroblast cell line, were irradiated with UVA (5 J/cm$^2$) and UVB (17-25 J/cm$^2$) in the presence of 101.8 mg/L apremilast. Results showed no cytotoxicity, suggesting that apremilast is not phototoxic.

## 5.R Outline of the review conducted by PMDA

### 5.R.1 Occurrence of vasculitis and perivasculitis

Regarding vasculitis and inflammation of perivascular connective tissue in various organs and tissues, which were observed as major findings in repeat-dose toxicity studies of apremilast in rodents, the applicant explained the mechanism of the occurrences of these findings and the extrapolatability to humans as follows:

The details of the mechanism of the occurrence of inflammation in perivascular connective tissue are unknown. However, it has been shown that administration of rolipram and roflumilast, compounds with PDE4-inhibitory activity, to mice and rats causes vasculitis and perivasculitis in the same tissues as those that showed inflammatory findings upon apremilast administration (*Toxicol Pathol.* 2008;36:827-39, *Pharmacol Toxicol.* 1996;78:44-9), which suggests that these findings were due to the class effect of compounds with PDE4-inhibitory activity. However, no inflammation was observed in vascular vessels or in perivascular connective tissue in toxicity studies of apremilast in monkeys. In clinical studies of apremilast, vasculitis-related events were observed in 1 subject in the apremilast 20 mg group (vasculitis) and in 2 subjects in the 30 mg group (cutaneous vasculitis and rheumatoid vasculitis [1 subject each]). A causal relationship to apremilast could not be ruled out for cutaneous vasculitis, but symptoms were mild and reversible. Rheumatoid vasculitis was severe in symptoms, but its causal relationship to apremilast was ruled out. After the market launch in foreign countries, apremilast was administered to 104,754 patients. There were 4 cases of vasculitis-related events (hypersensitivity vasculitis [2 events], temporal arteritis and vasculitis [1 event each]. Apremilast was discontinued in 3 of them. One patient continued the treatment and symptoms resolved). These findings suggest that apremilast does not cause any increase in the risk of vasculitis in humans and that the increased risk is specific to mice and rats.

The following results suggest that the particularly high sensitivity of mice and rats to the activity of apremilast to increase IL-6 expression is the cause for the inflammation of vascular vessels and perivascular connective tissue observed only in toxicity studies of mice and rats. Thus, it is considered that the apremilast-induced increase in plasma IL-6 production caused vasculitis, etc., in mice and rats.

- As shown in Table 10, apremilast at ≥0.1 μmol/L enhanced LPS-induced IL-6 production in the whole blood of rodents, whereas apremilast even at 10 μmol/L was ineffective in the whole blood of humans and monkeys.
- In a study which investigated the effect of apremilast (0.0001-100 μmol/L) on LPS-induced IL-6 production in human peripheral mononuclear cells, apremilast at ≥10 μmol/L enhanced IL-6 production (CTD 4.2.1.1.10). However, this apremilast concentration was approximately 14 times

the exposure ($C_{max}$, 334 ng/mL [ca. 0.7 μmol/L]) achieved following twice daily multiple dosing of apremilast (30 mg) to Japanese patients with psoriasis.

- There are no data suggestive of enhanced IL-6 production in clinical use. Also, increase in plasma IL-6 level was not observed in clinical studies.

**Table 10. Effect of apremilast on LPS-induced IL-6 production in whole blood derived from various animals**

| Apremilast concentration (μmol/L) | Human whole blood | Rat whole blood | Mouse whole blood | Monkey whole blood |
|---|---|---|---|---|
| 0 | 4512 | 609 | 597 | 2834 |
| 0.01 | 4628 | 325 | 569 | 2394 |
| 0.03 | 4138 | 212 | 795 | 2627 |
| 0.1 | 4251 | 723 | 1840 | 2397 |
| 0.3 | 4175 | 1177 | 2263 | 2477 |
| 1 | 4180 | 1915 | 3054 | 2214 |
| 3 | 4277 | 2397 | 3435 | 1775 |
| 10 | 4864 | 1886 | 3506 | 2091 |

Free IL-6 (pg/mL). LPS concentration was 1 ng/mL in human and monkey samples and 10 μg/mL in mouse and rat samples.
Cited from CTD 4.2.1.1.12

PMDA accepted the response of the applicant from a toxicological point of view. Currently, there is no clear risk of apremilast causing vasculitis in humans. However, taking account of the occurrences of vasculitis in foreign clinical studies and in the foreign post-marketing safety data, resulting in treatment discontinuation in some of the affected patients, PMDA considers that occurrences of vasculitis should be continuously investigated in the post-marketing surveillance, etc.

### 5.R.2 Embryo-fetal toxicity

Embryo-fetal toxicity studies showed increases in number of early resorptions and post-implantation losses, decreased fetal weight, and delayed ossification in mice and abortion in monkeys. The safety margin from the increases in number of early resorptions and post-implantation losses, abortion, etc., was 1.3 fold in mice and 1.4 fold in monkeys, failing to ensure a sufficiently wide safety margin. In addition, the mechanism of the occurrence of these findings is unclear. Therefore, PMDA instructed the applicant to contraindicate apremilast in pregnant women or women who may possibly be pregnant and to specify findings observed in studies on embryo-fetal development in the package insert. The applicant agreed with the indications and took appropriate actions.

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

The applicant submitted evaluation data, namely the results from a clinical pharmacology study in Japanese and non-Japanese subjects (Study CC-10004-CP-018), a mass balance study (Study CC-10004-PK-002), studies on intrinsic factors (Studies CC-10004-CP-019 and CC-10004-CP-029), a population pharmacokinetic analysis, a Through QT study (Study CC-10004-PK-008), etc. The applicant also submitted reference data, namely the results from a foreign bioavailability study (Study CC-10004-CP-012), a foreign food effect study (Study CC-10004-CP-022), studies on intrinsic factors (Studies CC-10004-CP-011 and CC-10004-CP-024), and studies on drug-drug interactions (Studies CC-10004-CP-020, CC-10004-CP-025, CC-10004-PK-005, and CC-10004-PK-010). Plasma apremilast concentration was determined by high-performance liquid chromatography-tandem mass spectrometry (lower limit of quantitation, 1.0 ng/mL). Radioactivity concentration of $^{14}$C-labeled apremilast was measured by high-performance liquid chromatography-accelerator mass spectrometry (lower limit of quantitation, 0.05 dpm/mL).

Unless specified otherwise, the dose of Otezla is expressed as that of apremilast, and pharmacokinetic parameters and observed values are expressed in mean value or mean ± SD.

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

#### 6.1.1 Absolute bioavailability (CTD 5.3.1.1.1, Study CC-10004-CP-012 [[redacted] to [redacted] 20[redacted]])

In a foreign 5-period cross-over study in healthy adult subjects, a single dose of apremilast (20 mg) was administered orally and, after 105 minutes (around time to reach maximum concentration ($t_{max}$) in oral administration), apremilast (100 μg) containing $^{14}$C-apremilast was intravenously administered

continuously to investigate the pharmacokinetics of apremilast. Table 11 shows the results. The absolute bioavailability was calculated to be 73.2%.

**Table 11. Pharmacokinetic parameters following a single oral administration of apremilast (20 mg) or following a single intravenous administration of apremilast (100 µg) containing $^{14}$C-apremilast**

| Dose/route of administration | $C_{max}$ (ng/mL) | $t_{1/2}$ (h) | $AUC_{inf}$ (ng·h/mL) | CL (mL/min) | Vz (L) | BA (%) |
|---|---|---|---|---|---|---|
| 100 µg, i.v. | 4.9 (27) | 6.2 ± 1.2 | 10.1 (23) | 169 ± 42 | 87.0 (23) | - |
| 20 mg, p.o. | 173 (27) | 7.6 ± 1.1 | 1480 (22) | 230 ± 46 | - | 73.2 |

Geometric mean (CV%); $t_{1/2}$ and clearance (CL), Mean ± SD; BA, Absolute bioavailability

### 6.1.2 Food effect (CTD 5.3.3.4.2, Study CC-10004-CP-022 [February to March 2012])

In a foreign 2-period cross-over study in 46 healthy adult subjects, a single dose of apremilast (30 mg) was administered orally under fasting conditions or after a meal to investigate the pharmacokinetics.

Pharmacokinetic parameters (geometric mean) following apremilast administration under fasting conditions and after a meal were as follows: $C_{max}$, 340 and 334 ng/mL, respectively; $AUC_t$, 3083 and 3436 ng·h/mL; $AUC_{inf}$, 3158 and 3506 ng·h/mL. The ratio of the pharmacokinetic parameters under fed conditions to that under fasted conditions (geometric least-squares mean ratio [90% confidence interval (CI)]) was 98.3% [90.7, 106.6] for $C_{max}$, 112.4% [109.3, 115.6] for $AUC_t$, and 112.0% [108.9, 115.1] for $AUC_{inf}$, from which it was concluded that food has little effect on the pharmacokinetics of apremilast.

## 6.2 Clinical pharmacology

### 6.2.1 Studies in healthy adult subjects

#### 6.2.1.1 Clinical pharmacology study in Japanese and non-Japanese subjects (CTD 5.3.3.3.2, Study CC-10004-CP-018 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In a 3-period cross-over study in Japanese, Chinese, and Caucasian healthy adult subjects (12 subjects each), a single dose of apremilast was administered orally. Table 12 shows pharmacokinetic parameters.

**Table 12. Pharmacokinetic parameters following a single oral administration of apremilast**

| Race (12 subjects each) | Dose | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_t$ (ng·h/mL) | $AUC_{inf}$ (ng·h/mL) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|
| Japanese | 20 mg | 221 ± 75 | 2.5 [1.0, 6.0] | 5.5 ± 0.9 | 1546 ± 326 | 1563 ± 321 | 13.3 ± 2.9 | 106 ± 26 |
| Chinese | | 212 ± 72 | 2.5 [1.0, 4.0] | 6.0 ± 1.4 | 1686 ± 616 | 1714 ± 624 | 13.0 ± 4.4 | 106 ± 20 |
| Caucasians | | 206 ± 53 | 2.5 [0.5, 6.0] | 7.1 ± 2.3 | 1811 ± 689 | 1856 ± 740 | 12.5 ± 5.2 | 119 ± 35 |
| Japanese | 40 mg | 353 ± 88 | 3.5 [2.0, 6.0] | 5.4 ± 0.9 | 2960 ± 504 | 2982 ± 505 | 13.8 ± 2.3 | 108 ± 29 |
| Chinese | | 329 ± 70 | 2.5 [1.0, 6.0] | 6.2 ± 1.2 | 3027 ± 886 | 3062 ± 916 | 14.1 ± 3.9 | 123 ± 29 |
| Caucasians | | 386 ± 90 | 3.0 [1.0, 6.0] | 7.3 ± 1.7 | 3855 ± 1455 | 3920 ± 1508 | 11.8 ± 4.9 | 117 ± 37 |

Mean ± SD; $t_{max}$, Median [range]

#### 6.2.1.2 Foreign clinical pharmacology study (CTD 5.3.3.1.1, Study CC-10004-PK-001 [[redacted] to [redacted] 20[redacted]])

In a foreign study in 40 healthy adult subjects, apremilast was administered orally as a single dose or as multiple doses for 5 days. Table 13 shows the pharmacokinetic parameters observed.

**Table 13. Pharmacokinetic parameters following a single oral dose, or once daily multiple oral dose of apremilast**

| Dose (6 subjects each) | Measuring time point | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{\tau}$ (ng·h/mL) | $C_{trough}$ (ng/mL) | CL/F (mL/min) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|
| 10 mg QD | Single dose | 214 ± 63 | 1.0 [0.5, 2.0] | 6.6 ± 1.3 | 1097 ± 167 | 6.9 ± 4.3 | 147 ± 28 | 84 ± 21 |
| | Multiple dose (Day 5) | 187 ± 57 | 2.0 [1.5, 2.5] | 5.5 ± 1.8 | 1019 ± 224 | 5.2 ± 2.8 | 171 ± 39 | 84 ± 42 |
| 20 mg QD | Single dose | 366 ± 140 | 1.8 [1.0, 4.0] | 4.6 ± 1.4 | 1969 ± 749 | 8.9 ± 7.4 | 186 ± 68 | 71 ± 26 |
| | Multiple dose (Day 5) | 446 ± 169 | 1.0 [1.0, 2.5] | 4.6 ± 1.3 | 2087 ± 857 | 6.5 ± 4.2 | 183 ± 68 | 73 ± 36 |
| 40 mg QD | Single dose | 560 ± 193 | 2.1 [1.5, 3.0] | 6.3 ± 2.1 | 3500 ± 1485 | 20.4 ± 9.3 | 215 ± 98 | 127 ± 103 |
| | Multiple dose (Day 5) | 546 ± 306 | 2.8 [2.0, 3.0] | 6.4 ± 3.6 | 3542 ± 1455 | 20.0 ± 11.8 | 219 ± 97 | 112 ± 53 |

Mean ± SD; $t_{max}$, Median [range]; QD, Once daily

### 6.2.1.3 Foreign clinical pharmacology study (CTD 5.3.3.1.3, Study CC-10004-PK-007 [[redacted] to [redacted] 20[redacted]])

In a foreign study in 55 healthy adult subjects, apremilast was orally administered for 14 days. Table 14 shows the pharmacokinetic parameters observed.

**Table 14. Pharmacokinetic parameters following a 14-day multiple oral administration of apremilast**

| Dose (9 subjects each) | Measuring time point | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{\tau}$ (ng·h/mL) | $C_{trough}$ (ng/mL) | CL/F (mL/min) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|
| 40 mg QD | Day 1[a)] | 436 ± 131 | 2.5 [1.5, 4.0] | 7.0 ± 1.7 | 3038 ± 1199 | - | 238 ± 87 | 144 ± 63 |
| | Day 14 | 582 ± 162 | 2.0 [1.5, 4.0] | 7.3 ± 1.9 | 4587 ± 1975 | 50 ± 37 | 169 ± 67 | 104 ± 40 |
| 60 mg QD | Day 1[a)] | 520 ± 132 | 3.0 [2.0, 4.0] | 8.3 ± 2.2 | 4230 ± 1627 | - | 241 ± 82 | 168 ± 67 |
| | Day 14 | 571 ± 208 | 3.0 [3.0, 3.0] | 8.5 ± 2.7 | 4668 ± 2078 | 52 ± 39 | 244 ± 78 | 176 ± 79 |
| 80 mg QD | Day 1 | 690 ± 275 | 4.0 [1.5, 8.0] | 7.0 ± 2.0 | 6183 ± 2174 | - | 218 ± 87 | 125 ± 36 |
| | Day 14 | 806 ± 253 | 3.0 [3.0, 4.0] | 9.7 ± 4.5 | 6362 ± 2236 | 66 ± 30 | 235 ± 88 | 204 ± 134 |
| 40 mg BID | Day 1[b)] | 375 ± 116 | 3.0 [2.0, 6.0] | - | 2410 ± 635 | - | - | - |
| | Day 14[c)] | 475 ± 111 | 3.0 [2.0, 8.0] | 6.3 ± 1.5 | 3577 ± 1015 | 178 ± 84 | 201 ± 61 | 106 ± 30 |

Mean ± SD; $t_{max}$, Median [range]; QD, Once daily; BID, Twice daily

a) $t_{1/2}$, CL/F, and Vz/F were calculated from data of 7 subjects.
b) Pharmacokinetic parameters after the initial dose
c) Pharmacokinetic parameters after dosing in the afternoon

### 6.2.1.4 Mass balance study (CTD 5.3.3.1.2, Study CC-10004-PK-002 [[redacted] 20[redacted]])

In a foreign study in 6 healthy adult subjects, a single dose of $^{14}$C-apremilast (20 mg) was administered orally to investigate pharmacokinetic parameters. $C_{max}$ was 527.5 ng eq/mL, $AUC_t$ was 6200.8 ng eq·h/mL, and elimination half-life ($t_{1/2}$) was 50.4 hours. The recovery of total radioactivity in urine and feces was 97.1% (57.9% in urine, 39.2% in feces), with radioactivity excretion being observed up to Day 3 in urine and up to Day 5 in feces. The main radioactive compounds detected in plasma were unchanged apremilast (44.8%) and M12 (38.7%) (percentage relative to total radioactivity in plasma), whereas most of those excreted were M12 (33.7%) in urine, and M9 (7.7%), M3 (4.6%), and unchanged apremilast (4.1%) in feces (percentage relative to the total radioactivity administered).

The ratio of $AUC_t$ of total radioactivity in the whole blood to that of radioactivity in plasma was 0.56, suggesting that apremilast and metabolites are scarcely distributed in blood cells. The optical isomer of apremilast (*R*-form) was not detected either in plasma or urine, suggesting that apremilast is unlikely to undergo isomerization in the body.

### 6.2.2 Studies in patients

#### 6.2.2.1 Japanese phase II study (CTD 5.3.3.5.6, Study CC-10004-PSOR-011 [July 2013 to December 2015])

In a Japanese phase II study in patients with psoriasis, apremilast was orally administered in multiple doses. Table 15 shows the pharmacokinetic parameters at Week 20 of administration.

**Table 15. Pharmacokinetic parameters under steady state (Week 20 of administration) in multiple dose administration of apremilast in patients with psoriasis**

| Dose (No. of patients) | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{\tau}$ (ng·h/mL) | $C_{trough}$ (ng/mL) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|
| 20 mg BID (n = 21) | 318 ± 98 | 2.0 [1.0, 4.0] | 4.7 ± 2.4[a)] | 2081 ± 709 | 96 ± 49 | 10.8 ± 5.1[a)] | 73 ± 29[a)] |
| 30 mg BID (n =20) | 391 ± 117 | 2.0 [1.0, 4.0] | 4.2 ± 1.1[b)] | 2571 ± 1,020 | 117 ± 79 | 13.6 ± 4.8[b)] | 87 ± 31[b)] |

Mean ± SD; $t_{max}$, Median [range]; BID, Twice daily
a) n = 11
b) n = 13

#### 6.2.2.2 Foreign phase II study (CTD 5.3.3.5.3, Study CC-10004-PSOR-005 [September 2008 to May 2015])

In a foreign phase II study in patients with psoriasis, apremilast was orally administered in multiple doses. Table 16 shows the pharmacokinetic parameters at Week 24 of administration.

**Table 16. Pharmacokinetic parameters of apremilast under steady state (Week 24 of administration) in multiple dose administration of apremilast in patients with psoriasis**

| Dose (No. of patients) | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{\tau}$ (ng·h/mL) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|
| 10 mg BID (n =5) | 254 ± 92 | 1.0 [1.0, 3.0] | 7.6 ± 4.1 | 1673 ± 664 | 7.3 ± 4.4 | 71 ± 58 |
| 20 mg BID (n = 4) | 248 ± 86 | 1.5 [1.0, 4.0] | 11.5 ± 7.2 | 2067 ± 369 | 9.9 ± 1.6 | 170 ± 127 |
| 30 mg BID (n = 3) | 679 ± 141 | 1.0 [0.5, 1.0] | 8.2 ± 2.4 | 4646 ± 1539 | 6.9 ± 1.9 | 79 ± 21 |

Mean ± SD; $t_{max}$, Median [range]; BID, Twice daily

### 6.2.3 Population pharmacokinetic/pharmacodynamic study (CTD 5.3.3.5.6)

A population pharmacokinetic analysis (NONMEM Version 7.3) was performed using data at 5752 points obtained from 517 subjects in a Japanese phase II study in patients with psoriasis (Study CC-10004-PSOR-011), phase I studies in healthy adult subjects (Studies CC-10004-BA-001, CC-10004-BA-002, CC-10004-PK-008, CC-10004-PK-010, CC-10004-CP-022, and CC-10004-CP-024), a foreign phase II study in patients with psoriasis (Study CC-10004-PSOR-005), and a foreign phase III study in patients with psoriasis (Study CC-10004-PSOR-008).

A one-compartment model incorporating the first order absorption process and the absorption lag time was constructed as the basic model and, as a result of the search for covariates,[3)] sex, disease, age, and race were selected as the covariates for CL/F and body weight as the covariate for Vc/F, and included in the final model. Pharmacokinetic parameters (inter-individual variability [%]) of apremilast estimated from the final model were 9.25 L/h (38.0) for CL/F, 115 L (27.1) for Vc/F, and 1.83 $h^{-1}$ (83.4) for Ka.

Table 17 shows the pharmacokinetic parameters under steady state in Japanese and non-Japanese subjects estimated from the final model.

**Table 17. Pharmacokinetic parameters (estimates) under steady state in Japanese and non-Japanese patients with psoriasis**

| Dose | Race (No. of patients) | $C_{max}$ (ng/mL) | $C_{trough}$ (ng/mL) | $AUC_{\tau}$ (ng·h/mL) |
|---|---|---|---|---|
| 20 mg BID | Japanese (n = 121)[a)] | 240 [107, 754] | 87 [32, 383] | 1939 [925, 6920] |
| | Non-Japanese (n = 121)[b)] | 248 [78, 622] | 116 [11, 399] | 2185 [451, 6295] |
| 30 mg BID | Japanese (n = 120)[a)] | 342 [185, 568] | 120 [40, 251] | 2727 [1348, 4792] |
| | Non-Japanese (n = 124)[b)] | 377 [152, 620] | 178 [64, 352] | 3337 [1296, 5777] |

Geometric mean [range]
a) Estimated based on the patient characteristics in Study CC-10004-PSOR-011
b) Estimated based on the patient characteristics in Study CC-10004-PSOR-005

[3)] Age, sex, body weight, ideal body weight, lean body weight, race (Japanese or non-Japanese), ethnicity, psoriasis (patients with psoriasis, healthy subjects, or other subjects) were evaluated as possible covariates for CL/F or Vc/F.

Based on the results of the population pharmacokinetic analysis and the efficacy data (number of patients achieving psoriasis area and severity index [PASI] 50 or PASI 75, 1433), the relationship between exposure and response was analyzed using the $E_{max}$ model with time and placebo effect taken into account. $E_{50}$[4)] ($AUC_{12h}$) achieving PASI 50 was estimated to be 1656 ng·h/mL, and $E_{50}$ ($AUC_{12h}$) achieving PASI 75 to be 1733 ng·h/mL.

### 6.2.4 Studies of intrinsic factors

#### 6.2.4.1 Effect of sex and age (CTD 5.3.3.3.4, Study CC-10004-CP-024 [February to April 2012])

In a foreign clinical pharmacology study in healthy adult subjects, a single dose of apremilast (30 mg) was administered orally to investigate the effect of sex and age on pharmacokinetics. Table 18 shows the results. The exposure tended to be higher in women than in men and in elderly subjects than in non-elderly subjects.

The applicant explained that, currently, there are no data that suggest a higher safety risk in elderly subjects or in women, as judged from the following observations: In the pooled subpopulation analysis, the relative incidence of gastrointestinal disorder-related events (apremilast group versus placebo group) tended to be higher in subjects aged ≥65 years than in subjects aged <65 years, and in women than in men, but (1) the types and severity of the observed adverse events were not significantly different between the groups of comparison, and (2) although serious adverse events and adverse events leading to treatment discontinuation tended to occur more frequently in elderly subjects and in women, there was no tendency of any specific event occurring frequently in these subject groups.

**Table 18. Pharmacokinetic parameters following a single-dose administration of apremilast (30 mg) to elderly/non-elderly men and women**

| | Age (years) | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{\tau}$ (ng·h/mL) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|
| Non-elderly men (n = 8) | 25-48 | 307 ± 56 | 2.5 [0.5, 5.0] | 8.5 ± 2.2 | 2702 ± 576 | 11.4 ± 2.5 | 137 ± 38 |
| Non-elderly women (n = 10) | 25-45 | 316 ± 102 | 2.3 [1.0, 5.0] | 10.1 ± 2.8 | 3117 ± 918 | 10.2 ± 3.5 | 155 ± 100 |
| Elderly men (n = 8) | 66-75 | 299 ± 50 | 2.3 [1.0, 5.0] | 7.6 ± 1.0 | 2705 ± 686 | 11.8 ± 3.6 | 129 ± 42 |
| Elderly women (n = 10) | 65-78 | 360 ± 108 | 4.0 [2.5, 5.1] | 10.4 ± 2.8 | 4080 ± 1434 | 8.1 ± 3.5 | 116 ± 49 |

Mean ± SD; $t_{max}$, Median [range]

#### 6.2.4.2 Effect of renal impairment (CTD 5.3.3.4.2, Study CC-10004-CP-022 [February to March 2012]; CTD 5.3.3.3.3, Study CC-10004-CP-019 [April to December 2011]; CTD 5.3.3.3.5, Study CC-10004-CP-029 [July to December 2013])

In foreign clinical pharmacology studies in subjects with mild, moderate, or severe renal impairment[5)] and subjects matched for characteristics other than renal function, pharmacokinetic parameters following a single oral administration of apremilast (30 mg) were as shown in Table 19. The geometric mean ratio [90% CI] of the pharmacokinetic parameters in subjects with moderate renal impairment to that in subjects with normal renal function was 87.5% [69.8, 109.7] for $C_{max}$ and 122.1% [93.6, 159.3] for $AUC_{inf}$, and the ratio in subjects with severe renal impairment relative to that in subjects with normal renal function was 141.6% [102.9, 194.8] for $C_{max}$ and 188.5% [132.5, 268.0] for $AUC_{inf}$. Regarding the main metabolite M12, the geometric mean ratio [90% CI] of the pharmacokinetic parameters in subjects with moderate renal impairment to that in subjects with normal renal function was 116.9% [81.9, 166.8] for $C_{max}$ and 161.4% [122.8, 212.3] for $AUC_{inf}$, and the ratio in subjects with severe renal impairment relative to that in subjects with normal renal function was 142.9% [106.3, 192.1] for $C_{max}$ and 291.7% [204.3, 416.4] for $AUC_{inf}$.

4) The exposure causing the half maximum effect of apremilast

5) Based on the eGFR (mL/min/1.73m$^2$) criteria, severity of renal impairment was defined as mild (≥60 and <90), moderate (≥30 and <60), and severe (<30).

**Table 19. Pharmacokinetic parameters following a single-dose administration of apremilast (30 mg) to subjects with renal impairment**

| | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{inf}$ (ng·h/mL) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|
| Subjects with mild renal impairment (n = 8)[a)] | 265 (30) | 3.0 [2.0, 4.0] | 8.4 (19) | 2975 (21) | 10.1 (21) | 122 (13) |
| Control for subjects with mild renal impairment (n = 8)[a)] | 249 (17) | 3.0 [2.0, 4.1] | 8.1 (24) | 3464 (19) | 8.7 (19) | 102 (36) |
| Subjects with moderate renal impairment (n = 8)[a)] | 182 (47) | 3.5 [0.5, 8.0] | 10.5 (40) | 3466 (67) | 8.7 (67) | 131 (49) |
| Control for subjects with moderate renal impairment (n = 8)[a)] | 208 (32) | 2.0 [1.0, 6.0] | 8.3 (24) | 2838 (24) | 10.6 (24) | 127 (21) |
| Subjects with severe renal impairment (n = 8)[b)] | 366 (35) | 3.0 [1.0, 6.0] | 11.8 (18) | 5425 (53) | 5.5 (53) | 95 (49) |
| Control for subjects with severe renal impairment (n = 7)[b)] | 255 (40) | 3.0 [2.0, 4.0] | 9.4 (18) | 2879 (18) | 10.4 (18) | 140 (22) |

Geometric mean (CV%); $t_{max}$, Median [range]; control, Population matched for characteristics other than renal function
a) CTD 5.3.3.3.5, Study CC-10004-CP-029
b) CTD 5.3.3.3.3, Study CC-10004-CP-019

#### 6.2.4.3 Effect of hepatic impairment (CTD 5.3.3.3.1, Study CC-10004-CP-011 [[redacted] to [redacted]])

In a foreign clinical pharmacology study in subjects with moderate (Child-Pugh 7-9) or severe (Child-Pugh 10-13) hepatic impairment (8 subjects for each severity group), and subjects matched for characteristics other than hepatic function (16 subjects), pharmacokinetic parameters following a single oral administration of apremilast was as shown in Table 20. The geometric mean ratio [90% CI] of the pharmacokinetic parameters in subjects with moderate hepatic impairment to that in subjects with normal hepatic function was 84.1% [59.7, 118.3] for $C_{max}$ and 94.6% [66.8, 133.8] for $AUC_{inf}$, and the ratio in subjects with severe hepatic impairment relative to that in subjects with normal hepatic function was 65.1% [46.3, 91.6] for $C_{max}$ and 98.4% [69.5, 139.2] for $AUC_{inf}$. Regarding the main metabolite M12, the geometric mean ratio [90% CI] of the pharmacokinetic parameters in subjects with moderate hepatic impairment to that in subjects with normal hepatic function was 107.7% [76.6, 151.3] for $C_{max}$ and 92.4% [72.1, 118.4] for $AUC_{inf}$, and the ratio in subjects with severe hepatic impairment relative to that in subjects with normal hepatic function was 89.2% [63.4, 125.3] for $C_{max}$ and 87.8% [68.6, 112.6] for $AUC_{inf}$.

**Table 20. Pharmacokinetic parameters following a single-dose administration of apremilast in subjects with hepatic impairment**

| | Dose | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$ (h) | $AUC_{inf}$ (ng·h/mL) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|
| Subjects with moderate impairment (n = 8) | 30 mg | 207 (43) | 2.5 [1.0, 9.0] | 10.0 (39) | 2897 (30) | 10.4 (30) | 150 (43) |
| Control for subjects with moderate impairment (n = 8) | | 246 (40) | 2.3 [1.0, 6.0] | 9.1 (23) | 3064 (55) | 9.8 (55) | 129 (36) |
| Subjects with severe impairment (n = 8) | 20 mg | 126 (62) | 2.5 [1.0, 6.0] | 12.4 (62) | 1968 (32) | 10.2 (32) | 181 (67) |
| Control for subjects with severe impairment (n = 8) | | 193 (29) | 2.3 [1.5, 6.0] | 8.0 (24) | 2000 (56) | 10.0 (57) | 115 (39) |

Geometric mean (CV%); $t_{max}$, Median [range]; control, Population matched for characteristics other than hepatic function

#### 6.2.5 Drug-drug interactions (CTD 5.3.3.4.4, Study CC-10004-PK-005 [[redacted] to [redacted]]; CTD 5.3.3.4.3, Study CC-10004-CP-025 [February to April 2012]; CTD 5.3.3.4.1, Study CC-10004-CP-020 [[redacted] to [redacted]]; CTD 5.3.3.4.5, Study CC-10004-PK-010 [[redacted] to [redacted]])

In light of the involvement of CYP3A4 in the metabolism of apremilast suggested in nonclinical pharmacokinetic studies [see "4.3.1.4 Study on CYP isoforms involved in the metabolism of apremilast"], drug-drug interactions with ketoconazole, a CYP3A4 inhibitor, and with rifampicin, a CYP3A4 inducer, were investigated. Also, drug-drug interactions in concomitant use of apremilast with an oral contraceptive (combination of ethinyl estradiol and norgestimate) and with methotrexate were investigated. Results are shown in Tables 21 and 22. Although the exposure to apremilast increased by approximately 36% when apremilast was concomitantly administered with ketoconazole, the applicant explained that the change was of little clinical significance, given the extent of inter-individual variability in the exposure observed in clinical studies.

**Table 21. Effect of concomitant drugs on the exposure to apremilast**

| Concomitant drug (dosage regimen) | Dosage regimen of apremilast | N | Method of administration | $C_{max}$ (ng/mL) | $AUC_t$ (ng·h/mL) | Geometric mean or geometric least-squares mean ratio (%) [90% CI] (concomitant use/apremilast alone) | |
|---|---|---|---|---|---|---|---|
| | | | | | | $C_{max}$ | $AUC_t$ or $AUC_\tau$ |
| Ketoconazole 400 mg once daily for 5 days | 20 mg single dose | 18 | Apremilast alone | 236 (29) | 2044 (32) | 104.9 [92.2, 119.3] | 136.8 [126.6, 147.7] |
| | | | Concomitant use | 247 (31) | 2795 (32) | | |
| Rifampicin 600 mg single dose i.v.[a)] | 30 mg single dose | 21 | Apremilast alone | 290 (25) | 3070 (31) | 113.1 [103.2, 123.9] | 96.4 [88.6, 104.8] |
| | | 19 | Concomitant use | 331 (25) | 2940 (31) | | |
| Rifampicin 600 mg p.o. once daily for 14 days | 30 mg single dose | 21 | Apremilast alone | 290 (25) | 3070 (31) | 56.8 [51.8, 62.3] | 27.9 [25.6, 30.3] |
| | | 19 | Concomitant use | 166 (23) | 850 (34) | | |
| Methotrexate 15 mg single dose | 30 mg twice daily for 5 days | 15 | Apremilast alone | 554 (35) | 3670 (54)[b)] | 95.0 [87.9, 102.7] | 99.3 [92.8, 106.2] |
| | | | Concomitant use | 526 (42) | 3660 (57)[b)] | | |

Geometric mean (CV%)
Ketoconazole, CTD 5.3.3.4.4, Study CC-10004-PK-005; rifampicin, CTD 5.3.3.4.3, Study CC-10004-CP-025; methotrexate, CTD 5.3.3.4.5, Study CC-10004-PK-010
a) Rifampicin was administered at 5 minutes after apremilast administration.
b) Evaluated by $AUC_\tau$

**Table 22. Effect of apremilast on the exposure to concomitant drugs**

| Concomitant drug (dosage regimen) | Dosage regimen of apremilast | Analyte | N | Method of administration | $C_{max}$ (ng/mL) | $AUC_\tau$ (ng·h/mL) | Geometric mean ratio (%) [90% CI] (concomitant drug alone/concomitant use of apremilast) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | $C_{max}$ | $AUC_\tau$ |
| Ethinyl estradiol/ norgestimate Once daily for 21 days | 30 mg twice daily for 10 days | Ethinyl estradiol | 38 | Ethinyl estradiol/ norgestimate alone | 132 (30) [c)] | 1213 (35) [d)] | 91.3 [86.1, 96.9] | 88.8 [83.6, 94.3] |
| | | | 35 | Concomitant use of apremilast | 121 (31) [c)] | 1063 (34) [d)] | | |
| | | 17-Deacetylnorgestimate[a)] | 38 | Ethinyl estradiol/ norgestimate alone | 2.1 (22) | 20.5 (25) | 90.0 [85.0, 95.3] | 89.3 [85.9, 92.8] |
| | | | 35 | Concomitant use of apremilast | 1.9 (19) | 18.1 (22) | | |
| Methotrexate 15 mg single dose | 30 mg twice daily for 5 days | Methotrexate | 6 | Methotrexate alone | 411 (28) | 1650 (40) | 99.5 [92.7, 106.8] | 100.4 [92.9, 108.5] |
| | | | | Concomitant use of apremilast | 396 (32) | 1670 (32) | | |
| | | 7-Hydroxymethotrexate[b)] | | Methotrexate alone | 59 (50) | 1230 (47) | 104.0 [92.8, 116.6] | 98.2 [86.9, 111.1] |
| | | | | Concomitant use of apremilast | 62 (40) | 1210 (38) | | |

Geometric mean (CV%)
a) Metabolite of norgestimate
b) Metabolite of methotrexate
c) Unit, pg/mL
d) Unit, pg·h/mL

### 6.2.6 Pharmacodynamics

#### 6.2.6.1 Effect on QTc interval (CTD 5.3.3.1.4, Study CC-10004-PK-008 [[redacted] to [redacted] 20[redacted]])

In a foreign double-blind, randomized, 4-period cross-over study in 60 healthy adult subjects, apremilast (30, 50 mg) or placebo was administered twice daily for 5 days to investigate the effect on QTc interval. Subjects in the positive control group received moxifloxacin (400 mg).

The difference [90% CI] in the change in the least squares mean of QTcI[6)] from baseline in the apremilast 30 or 50 mg group from that in the placebo group on Day 5 of administration (up to 23 hours after administration) was −4.2 msec [−6.5, −1.8] at the maximum in the 30 mg group and −4.6 msec [−6.9, −2.2] at the maximum in the 50 mg group. The difference [90% CI] in the change in the least squares mean of QTcI from baseline in the moxifloxacin group from that in the placebo group was 9.3 msec [5.9, 12.6] at the maximum. The change (least squares mean) in QTcF[7)] from baseline was 0.4 msec [−1.8, 2.6] at the maximum in the 30 mg group and 0.0 msec [−2.1, 2.2] at the maximum in the 50 mg group.

6) QTc interval calculated based on RR interval corrected for each subject
7) QT interval corrected by Fridericia's method

$C_{max}$ and $AUC_{\tau}$ (mean [range]) on Day 5 of administration were 375 ng/mL [153, 717] and 2402 ng·h/mL [1161, 5443], respectively, in the apremilast 30 mg group and 532 ng/mL [239, 1062] and 3700 ng·h/mL [1632, 9350], respectively, in the 50 mg group.

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Ethnic difference of the pharmacokinetics of apremilast

The applicant's explanation on the effect of ethnic factors on the pharmacokinetics of apremilast:
In a clinical pharmacology study in Japanese, Chinese, and Caucasian healthy subjects (Study CC-10004-CP-018), apremilast was administered orally as a single dose. As a result, the geometric mean ratios [90% CI] of $C_{max}$ and $AUC_{inf}$ in Japanese subjects to those in Caucasian subjects were 104.9% [87.6, 125.6] and 88.9% [71.1, 111.3], respectively, in the apremilast 20 mg group and 91.0% [76.0, 109.0] and 80.5% [64.3, 100.7], respectively, in the 40 mg group. As shown in Table 17, $AUC_{\tau}$ (mean [range]) in multiple dose administration of apremilast (30 mg), estimated from the population pharmacokinetic analysis, in Japanese and foreign patients with psoriasis was 2727 [1348, 4792] and 3337 [1296, 5777] ng·h/mL, respectively, showing a lower tendency of exposure to apremilast in Japanese patients. However, in light of the observations that, in Study CC-10004-CP-018, 90% CI of the geometric mean ratio included the value "100%" and that, in the population pharmacokinetic analysis of patients with psoriasis, the exposure in the Japanese population was within the range observed in the non-Japanese population, the applicant considered that ethnic factors do not significantly affect the pharmacokinetics of apremilast.

PMDA concluded that the lower tendency of exposure to apremilast in Japanese population than in non-Japanese population was of no clinical significance because (1) there is no clear tendency of reduced efficacy of apremilast in Japanese population, as judged from Table 23, and (2) there is no clear difference in the incidence of adverse events between Japanese and non-Japanese populations [see "7.R.3 Safety"].

**Table 23. Rate of achieving PASI 50, 75, 90, and sPGA at Week 16 of administration (efficacy analysis population, LOCF)**

| | Study CC-10004-PSOR-011 | | Study CC-10004-PSOR-005 | | Pooled data of Studies CC-10004-PSOR-008 and CC-10004-PSOR-009 | |
|---|---|---|---|---|---|---|
| | Placebo | 30 mg | Placebo | 30 mg | Placebo | 30 mg |
| Rate of achieving PASI 50 | 21.4 (18/84) | 50.6 (43/85) | 25.0 (22/88) | 60.2 (53/88) | 17.9 (75/419) | 57.7 (482/836) |
| Rate of achieving PASI 75 | 7.1 (6/84) | 28.2 (24/85) | 5.7 (5/88) | 40.9 (36/88) | 5.5 (23/419) | 31.7 (265/836) |
| Rate of achieving PASI 90 | 1.2 (1/84) | 14.1 (12/85) | 1.1 (1/88) | 11.4 (10/88) | 0.7 (3/419) | 9.4 (79/836) |
| Rate of achieving sPGA (0 or 1) | 8.8 (6/68) | 29.6 (21/71) | 12.6 (11/87) | 33.7 (28/83) | 4.1 (17/419) | 21.3 (178/836) |

% (number of subjects)

### 6.R.2 Pharmacokinetics in patients with renal or hepatic impairment

The applicant's explanation on the effect of renal or hepatic impairment on the pharmacokinetics of apremilast:
In Studies CC-10004-CP-019 and CC-10004-CP-029 which investigated the effect of renal impairment on the pharmacokinetics of apremilast, the geometric mean ratios [90% CI] of $AUC_{inf}$ in subjects with mild, moderate, or severe renal impairment to that in subjects with normal renal function were 85.9% [65.8, 112.0], 122.1% [93.6, 159.3], and 188.5% [132.5, 268.0], respectively, showing a tendency of increase in the exposure to apremilast with the increase in the severity of renal impairment. In clinical studies in patients with psoriasis vulgaris and psoriatic arthritis,[8)] safety in subjects with mild or moderate renal impairment was investigated. As shown in Table 24, there was no safety concern. Based on the above, the applicant considered it unnecessary to adjust the dose of apremilast in patients with mild to moderate renal impairment.

8) In clinical studies of apremilast, subjects with severe renal impairment were excluded.

**Table 24. Safety of apremilast (30 mg) in subjects classified by renal function**

| | PSOR Phase 3 Pool[a)] | | | PSA Phase 3 Pool[b)] | | |
|---|---|---|---|---|---|---|
| | Normal (n = 1070) | Mild impairment (n = 103) | Moderate impairment (n = 10) | Normal (n = 822) | Mild impairment (n = 136) | Moderate impairment (n = 15) |
| All adverse events | 890 (83.2) | 88 (85.4) | 9 (90.0) | 690 (83.9) | 112 (82.4) | 12 (80.0) |
| Diarrhoea | 182 (17.0) | 19 (18.4) | 3 (30.0) | 133 (16.2) | 23 (16.9) | 6 (40.0) |
| Nausea | 170 (15.9) | 21 (20.4) | 3 (30.0) | 138 (16.8) | 20 (14.7) | 3 (20.0) |
| Upper respiratory tract infection | 216 (20.2) | 13 (12.6) | 1 (10.0) | 101 (12.3) | 17 (12.5) | 1 (6.7) |
| Nasopharyngitis | 178 (16.6) | 16 (5.5) | 1 (10.0) | 88 (10.7) | 12 (8.8) | 0 |
| Headache | 76 (7.1) | 7 (6.8) | 2 (20.0) | 102 (12.4) | 19 (14.0) | 1 (6.7) |
| Serious adverse events | 88 (8.2) | 17 (16.5) | 4 (40.0) | 123 (15.0) | 27 (19.9) | 1 (16.7) |

Number of subjects (%)

a) Pooled analysis of Studies CC-10004-PSOR-008 and CC-10004-PSOR-009

b) Pooled analysis of Studies CC-1004-PSA-002, CC-1004-PSA-003, CC-1004-PSA-004, and CC-1004-PSA-005

In Study CC-10004-CP-019, the exposure to apremilast in subjects with severe renal impairment was approximately twice that in subjects with normal renal function. Also, as shown in Table 25, the results of the population pharmacokinetic analysis suggested that the exposure to apremilast in patients with psoriatic arthritis with normal renal function receiving apremilast 30 mg twice daily is similar to that in subjects with severe renal impairment receiving apremilast 30 mg once daily. From these findings, the applicant considered that the dose of apremilast should be decreased to 30 mg once daily administration in patients with severe renal impairment.

**Table 25. Pharmacokinetic parameters (estimates) in multiple dose administration of apremilast in patients with normal renal function or severe renal impairment**

| | $C_{max}$ (ng/mL) | $t_{1/2}$ (h) | $AUC_{24h}$ (ng·h/mL) |
|---|---|---|---|
| Patients with psoriasis with normal renal function Apremilast 30 mg BID[a)] | 450 [225, 781] | 9.2 [6.2, 11.4] | 8167 [3738, 14,940] |
| Subjects with severe renal impairment Apremilast 30 mg QD[b)] | 533 [263, 924] | 11.7 [9.3, 12.9] | 7991 [3566, 14,903] |

Mean [90% CI]; BID, Twice daily; QD, Once daily

a) Estimated from population pharmacokinetic analysis based on the data of Study C-10004-PSA-002

b) Estimated from population pharmacokinetic analysis based on the data of Study C-10004-CP-019

In Study CC-10004-CP-011 in subjects with hepatic impairment, $AUC_{inf}$ (geometric mean) after apremilast administration in subjects with severe hepatic impairment and in subjects with normal hepatic function was 1967.8 and 2000.2 ng·h/mL, respectively, showing a similar value in both subject groups. Therefore, the applicant considered it unnecessary to adjust the dose of apremilast in patients with hepatic impairment.

PMDA's view:

Although the exposure to apremilast shows a tendency of increase with the severity of renal impairment, no clinically significant events were observed in subjects receiving apremilast >30 mg twice daily in clinical studies in healthy adult subjects (Studies CC-10004-PK-001, CC-10004-PK-007, etc.). Also, although apremilast 30 mg once daily treatment is recommended in the US and in Europe in patients with psoriasis with severe renal impairment, there are no efficacy or safety data available on this dosage regimen, precluding the evaluation of risk-benefit balance. Thus, PMDA is disinclined to uniformly recommend apremilast 30 mg once daily treatment to patients with severe renal impairment. The following caution statement is required: Apremilast should be administered with care with dose reduction in mind and patients should be closely monitored after administration. Also, information on the efficacy and safety of apremilast in patients with renal or hepatic impairment should be continuously collected.

The above conclusion by the PMDA will be finalized, taking account of comments raised in the Expert Discussion.

### 6.R.3 Drug-drug interactions

Based on the pharmacokinetic interactions observed between apremilast and CYP3A4-inducing drugs and with CYP3A4-inhibiting drugs, the applicant explained the possible drug-drug interactions between

apremilast and conventional anti-psoriatic drugs that are expected to be concomitantly administered with apremilast, as follows:
In Japan, drugs used for the systemic treatment of psoriasis include, among others, biological products (ustekinumab [genetical recombination], adalimumab [genetical recombination], infliximab [genetical recombination], secukinumab [genetical recombination], etc.), corticosteroids, and cyclosporine.

Biological products are degraded by proteases and are therefore unlikely to directly cause drug-drug interactions with apremilast.

Prednisone, a corticosteroid preparation, is metabolized by CYP3A4, but does not affect CYP3A4 activity (*J Clin Pharmacol*. 2014;54:1280-9), suggesting that it is unlikely to cause drug-drug interaction with apremilast.

Cyclosporine inhibits CYP3A4, P-gp, OATP1B1, OATP1B3, and OATP2B1. However, concomitant use of apremilast with ketoconazole, a drug with CYP3A4- and P-gp-inhibiting activities, did not cause a clinically significant increase in the exposure to apremilast. Also, *in vitro* studies showed that apremilast is not a substrate of OATP1B1 or OATP1B3 [see "4.5.2 Transporters"].

Based on the above, concomitant use of apremilast with conventional anti-psoriatic drugs is unlikely to cause any clinically significant drug-drug interactions, as judged from a clinical pharmacological point of view. However, since the pharmacokinetics of apremilast is affected by concomitant use with drugs with CYP3A4-inducing activity, a caution statement will be included in the package insert regarding the concomitant use with drugs with CYP3A4-inducing activity.

PMDA understands the explanation of the applicant. However, because of the limited data available on the effect of concomitant drugs, it is practically impossible currently to draw any conclusion on the safety of concomitant use [see "7.R.5.2 Concomitant use with conventional therapies"]. Further information should be collected in the post-marketing surveillance, etc.

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

The applicant submitted the efficacy and safety evaluation data, namely the results from a Japanese phase II study (Study CC-10004-PSOR-011), a foreign phase II study (Study CC-10004-PSOR-005), and foreign phase III studies (Studies CC-10004-PSOR-008 and CC-10004-PSOR-009) on psoriasis vulgaris or psoriatic arthritis with moderate to severe plaque rash; and foreign phase III studies in patients with psoriatic arthritis (Studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005). The applicant also submitted the reference data, namely the results from foreign clinical studies in patients with psoriasis vulgaris or psoriatic arthritis with moderate to severe plaque rash (Studies CC-10004-PSOR-003 and CC-10004-PSOR-010) and a foreign clinical study in patients with psoriatic arthritis (Study CC-10004-PSA-001).

### 7.1 Phase I study

#### 7.1.1 Phase I study (CTD 5.3.3.1.3, Study CC-10004-PK-007 [[redacted] to [redacted] 20[redacted]]

A placebo-controlled, randomized, double-blind, dose titration study was conducted to investigate the safety of apremilast in healthy adult subjects (target sample size, 55 subjects) in the UK.

The subjects were to orally receive apremilast (40, 60, 80 mg) once daily for 14 days (QD group), apremilast 40 mg twice daily for 14 days (BID group), or apremilast 10 mg once daily from Day 1 to Day 3, 20 mg once daily from Day 4 to Day 6, and 40 mg once daily from Day 7 to Day 14 (dose titration group).

All of the 55 randomized subjects (11 per group, including 2 receiving placebo per group) were included in the safety analysis population.

Adverse events were reported by 7 of 9 subjects in the 40 mg QD group, 9 of 9 subjects in the 60 mg QD group, 9 of 9 subjects in the 80 mg QD group, 9 of 9 subjects in the 40 mg BID group, 8 of 9 subjects in the dose titration group, and 5 of 10 subjects receiving placebo. Table 26 shows the main events reported. Neither deaths nor serious adverse events were reported.

An adverse event leading to discontinuation was reported by 1 subject receiving placebo (toothache).

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were reported by 7 of 9 subjects in the 40 mg QD group, 8 of 9 subjects in the 60 mg QD group, 9 of 9 subjects in the 80 mg QD group, 9 of 9 subjects in the 40 mg BID group, 6 of 9 subjects in the dose titration group, and 3 of 10 subjects receiving placebo.

**Table 26. Adverse events reported by ≥2 subjects in any group (safety analysis population)**

| | 40 mg QD (n = 9) | 60 mg QD (n = 9) | 80 mg QD (n = 9) | 40 mg BID (n = 9) | Dose titration (n = 9) | Placebo (n = 10) |
|---|---|---|---|---|---|---|
| Nausea | 7 (78) | 6 (67) | 7 (78) | 8 (89) | 4 (44) | 1 (10) |
| Headache | 3 (33) | 4 (44) | 6 (67) | 8 (89) | 6 (67) | 1 (10) |
| Diarrhoea | 2 (22) | 3 (33) | 1 (11) | 1 (11) | 1 (11) | 0 |
| Dizziness | 1 (11) | 2 (22) | 3 (33) | 3 (33) | 0 | 1 (10) |
| Abdominal pain upper | 1 (11) | 1 (11) | 2 (22) | 4 (44) | 2 (22) | 0 |
| Pharyngolaryngeal pain | 1 (11) | 0 | 0 | 0 | 2 (22) | 1 (10) |
| Fatigue | 0 | 2 (22) | 1 (11) | 2 (22) | 0 | 0 |
| Vomiting | 0 | 0 | 4 (44) | 1 (11) | 1 (11) | 0 |
| Haematuria | 0 | 0 | 2 (22) | 0 | 0 | 0 |
| Abdominal distension | 0 | 0 | 1 (11) | 0 | 0 | 2 (20) |
| Dyspepsia | 0 | 0 | 0 | 2 (22) | 0 | 0 |
| Abdominal pain lower | 0 | 0 | 0 | 0 | 2 (22) | 0 |
| Back pain | 0 | 0 | 0 | 0 | 2 (22) | 0 |

Number of subjects (%)

Based on the lower tendency of the incidence of gastrointestinal disorder-related events in the dose titration group than in the fixed dose groups in the above phase I study (Study CC-10004-PK-007), the applicant explained that the dose titration method should be selected for safety purposes.

## 7.2 Phase II studies

### 7.2.1 Foreign phase II study (CTD 5.3.5.1.1, Study CC-10004-PSOR-003 [April 2006 to February 2007])

A placebo-controlled, randomized, double-blind, parallel group study was conducted to investigate the efficacy and safety of apremilast in patients with psoriasis vulgaris or psoriatic arthritis with moderate to severe plaque rash[9)] (target sample size, 255 subjects [85 per group]) in Canada, Germany, and the Czech Republic.

The subjects were to orally receive apremilast 20 mg once daily, apremilast 20 mg twice daily, or placebo, for 12 weeks.

All of the 260 randomized subjects (87 in the 20 mg QD group, 86 in the 20 mg BID group, 87 in the placebo group) were included in the intent-to-treat (ITT) population, and the ITT population was used for the efficacy analysis. Of these, 259 subjects (87 in the 20 mg QD group, 85 in the 20 mg BID group, 87 in the placebo group), except 1 subject who did not receive the study drug, were included in the safety analysis. Study discontinuation occurred in 19.5% (17 of 87) of subjects in the 20 mg QD group, 12.9% (11 of 86) of subjects in the 20 mg BID group, and 21.8% (19 of 87) of subjects in the placebo group. The main reasons for the discontinuation included adverse events (5.7% [5 of 87] in the 20 mg QD group, 3.5% [3 of 86] in the 20 mg BID group, 8.0% [7 of 87] in the placebo group) and inadequate response (5.7% [5 of 87] in the 20 mg QD group, 3.5% [3 of 86] in the 20 mg BID group, 5.7% [5 of 87] in the placebo group).

Table 27 shows the percentage of subjects achieving ≥75% reduction form baseline in PASI score (PASI 75 response rate) at Week 12 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and the apremilast 20 mg BID group. Table 27 also shows the percentage of subjects achieving ≥50% or ≥90% reduction form baseline in PASI score (PASI 50 and 90 response rates, respectively) at Week 12 of administration, the secondary endpoints.

9) Subjects who met both of the following criteria: (a) PASI score ≥10 and the area of plaque rash ≥10% of the body surface area and (b) systemic therapy or phototherapy deemed necessary by the physician

**Table 27. PASI 50, 75, and 90 response rates at Week 12 of administration (ITT, LOCF)**

| | 20 mg QD | 20 mg BID | Placebo | Difference from placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg QD group | 20 mg BID group |
| PASI 50 response rate | 27.6 (24/87) | 57.0 (49/86) | 23.0 (20/87) | | |
| PASI 75 response rate | 10.3 (9/87) | 24.4 (21/86) | 10.3 (9/87) | 0.0 [−9.1, 9.1]<br>*P* = 1.000 | 14.1 [3.0, 25.2]<br>*P* = 0.023 |
| PASI 90 response rate | 2.3 (2/87) | 14.0 (12/86) | 5.7 (5/87) | | |

% (number of subjects)
a) Chi-square test with continuous correction
b) Adjusted for multiplicity using Bonferroni's method

Adverse events were reported by 67.8% (59 of 87) of subjects in the 20 mg QD group, 54.1% (46 of 85) of subjects in the 20 mg BID group, and 59.8% (52 of 87) of subjects in the placebo group. Table 28 shows the main events reported. No death occurred.

Serious adverse events were reported by 1.1% (1 of 87) of subjects in the 20 mg QD group (knee ligament repair/meniscus lesion), 1.2% (1 of 25) of subjects in the 20 mg BID group (psoriasis aggravated), and 5.7% (5 of 87) of subjects in the placebo group (alcoholism, panic attack, psoriasis aggravated, rehabilitation therapy, and pregnancy test positive). The causal relationship of panic attack to the study drug could not be ruled out, but the outcome was recovery.

Adverse events leading to discontinuation were reported by 8.0% (7 of 87) of subjects in the 20 mg QD group, 3.5% (3 of 85) of subjects in the 20 mg BID group, and 8.0% (7 of 87) of subjects in the placebo group. The main event was headache (3 subjects in the 20 mg QD group).

Adverse drug reactions were reported by 29.9% (26 of 87) of subjects in the 20 mg QD group, 23.5% (20 of 85) of subjects in the 20 mg BID group, and 25.3% (22 of 87) of subjects in the placebo group.

**Table 28. Adverse events reported by ≥3% of subjects in the apremilast group (safety analysis population)**

| | 20 mg QD (n = 87) | 20 mg BID (n = 85) | Placebo (n = 87) |
|---|---|---|---|
| Headache | 16 (18.4) | 11 (12.9) | 9 (10.3) |
| Nasopharyngitis | 12 (13.8) | 12 (14.1) | 12 (13.8) |
| Diarrhoea | 9 (10.3) | 5 (5.9) | 2 (2.3) |
| Pruritus | 5 (5.7) | 4 (4.7) | 5 (5.7) |
| Fatigue | 5 (5.7) | 1 (1.2) | 5 (5.7) |
| Nausea | 3 (3.4) | 5 (5.9) | 0 |
| Arthralgia | 3 (3.4) | 2 (2.4) | 0 |
| Antinuclear factor positive | 3 (3.4) | 1 (1.2) | 1 (1.1) |
| Hypertension | 3 (3.4) | 0 | 0 |
| Cough | 1 (1.1) | 3 (3.5) | 1 (1.1) |
| Pain in extremity | 0 | 3 (3.5) | 0 |

Number of subjects (%)

### 7.2.2 Japanese phase II study (CTD 5.3.5.1.6, Study CC-10004-PSOR-011 [July 2013 to December 2015]) (bridging study)

A placebo-controlled, randomized, double-blind, parallel group study was conducted to investigate the efficacy and safety of apremilast in patients with psoriasis vulgaris or psoriatic arthritis with moderate to severe plaque rash[10)] (target sample size, 246 subjects [82 per group]).

The study consisted of 2 periods (placebo-controlled period until Week 16 and apremilast administration period from Week 16 to Week 68). The treatment was to be started by the gradual dose increase as shown in Table 29, followed by twice daily oral administration of apremilast 20 mg, 30 mg, or placebo for 16 weeks. From Week 16 on, subjects who had been assigned to the placebo group were to be reassigned

10) Subjects who met both of the following criteria: (a) PASI score ≥12 at screening and baseline and the area of plaque rash ≥10% of the body surface area and (b) inappropriate for topical therapy or treated with one or more topical therapies for 4 weeks.

to the apremilast 20 or 30 mg group, and subjects who had been assigned to either of the apremilast groups were to be continuously treated with the same dosage regimen.

**Table 29. Schedule for gradual dose increase in the apremilast groups**

| | Day 1 | Day 2 | Day 3 | Day 4 [b)] | Day 5 | Day 6 and thereafter |
|---|---|---|---|---|---|---|
| Morning[a)] | 10 mg | 10 mg | 10 mg | 20 mg | 20 mg | 30 mg |
| Evening[a)] | Placebo | 10 mg | 20 mg | 20 mg | 30 mg | 30 mg |

a) The study drug was to be administered at intervals of approximately 12 hours without regard to meals.
b) In the 20 mg group, the same dose (20 mg) was administered from Day 4 on.

Of 254 subjects (85 in the 20 mg group, 85 in the 30 mg group, 84 in placebo group) subjected to randomization using the diagnosis of psoriatic arthritis (yes, no), drug concentration measurement for population pharmacokinetics (yes, no), and drug concentration measurement for the standard pharmacokinetic analysis (yes, no) as the strata, all of subjects who received the study drug were included in the modified Intent-to treat (mITT) population and the safety analysis population, and the mITT population was used for the efficacy analysis.

During the placebo-controlled period, study discontinuation occurred in 18.8% (16 of 85) of subjects in the 20 mg group, 10.6% (9 of 85) of subjects in the 30 mg group, and 14.3% (12 of 84) of subjects in the placebo group. The main reasons for the discontinuation were adverse events (11.8% [10 of 85] in the 20 mg group, 7.1% [6 of 85] in the 30 mg group, 3.6% [3 of 84] in the placebo group) and inadequate response (2.4% [2 of 85] in the 20 mg group, 2.4% [2 of 85] in the 30 mg group, 1.2% [1 of 84] in the placebo group). Of 217 subjects who completed the placebo-controlled period, 216 subjects (36 in the placebo/20 mg group, 35 in the placebo/30 mg group, 69 in the continuous 20 mg group, 76 in the continuous 30 mg group) proceeded to the apremilast administration period.

Table 30 shows the PASI 75 response rate at Week 16 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of the apremilast 20 and 30 mg groups. Table 30 also shows the PASI 50, PASI 90, and static physician global assessment (sPGA) (0 or 1) response rates at Week 16 of administration, the secondary endpoints.

**Table 30. PASI 50, 75, 90 and sPGA response rates (mITT, LOCF) at Week 16 of administration**

| | 20 mg | 30 mg | Placebo | Difference from placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg group | 30 mg group |
| PASI 50 response rate | 41.2 (35/85) | 50.6 (43/85) | 21.4 (18/84) | 19.7 [6.1, 33.4] | 29.2 [15.4, 42.9] |
| PASI 75 response rate | 23.5 (20/85) | 28.2 (24/85) | 7.1 (6/84) | 16.4 [5.8, 27.0] *P* = 0.0032 | 21.1 [10.1, 32.1] *P* = 0.0003 |
| PASI 90 response rate | 7.1 (6/85) | 14.1 (12/85) | 1.2 (1/84) | 5.9 [-0.1, 11.8] | 12.9 [5.2, 20.7] |
| sPGA (0 or 1) response rate[c)] | 23.9 (17/71) | 29.6 (21/71) | 8.8 (6/68) | 15.1 [3.1, 27.1] | 20.8 [8.2, 33.3] |

% (number of subjects)
a) Chi-square test
b) Adjusted for multiplicity using Hochberg's method
c) Analysis was performed on subjects who showed sPGA score of ≥3 at baseline.

During the placebo-controlled period, adverse events were reported by 57.6% (49 of 85) of subjects in the 20 mg group, 51.8% (44 of 85) of subjects in the 30 mg group, and 41.7% (35 of 84) of subjects in the placebo group. Table 31 shows the main events reported. No death occurred.

Serious adverse events were reported by 4.7% (4 of 85) of subjects in the apremilast 20 mg group (arthritis bacterial, cerebral haemorrhage, coronary artery stenosis, and cholelithiasis). The causal relationship of arthritis bacterial and cerebral haemorrhage to the study drug could not be ruled out, but the outcome was recovery for all of them.

Adverse events leading to discontinuation were reported by 11.8% (10 of 85) of subjects in the 20 mg group, 7.1% (6 of 85) of subjects in the 30 mg group, and 4.8% (4 of 84) of subjects in the placebo group. The main adverse event was psoriasis (3 subjects in the 20 mg group, 4 subjects in the 30 mg group, and 2 subjects in the placebo group).

Adverse drug reactions were reported by 21.2% (18 of 85) of subjects in the 20 mg group, 29.4% (25 of 85) of subjects in the 30 mg group, and 9.5% (8 of 84) of subjects in the placebo group.

**Table 31. Adverse events reported by ≥3% of subjects in either of the apremilast groups during the placebo-controlled period (safety analysis population)**

| | 20 mg (n = 85) | 30 mg (n = 85) | Placebo (n = 84) |
|---|---|---|---|
| Nasopharyngitis | 10 (11.8) | 10 (11.8) | 7 (8.3) |
| Diarrhoea | 7 (8.2) | 8 (9.4) | 1 (1.2) |
| Abdominal discomfort | 1 (1.2) | 6 (7.1) | 1 (1.2) |
| Psoriasis | 3 (3.5) | 4 (4.7) | 2 (2.4) |
| Insomnia | 4 (4.7) | 2 (2.4) | 0 |

Number of subjects (%)

During the period up to Week 72 of administration, adverse events were reported by 77.7% (94 of 121) of subjects receiving 20 mg (20 mg cohort), 74.2% (89 of 120) of subjects receiving 30 mg (30 mg cohort). Table 32 shows the main events reported.

One subject in the 20 mg cohort died of metastatic lung cancer,[11)] for which a causal relationship to the study drug could not be ruled out.

Serious adverse events were reported by 9.1% (11 of 121) of subjects in the 20 mg cohort (cholelithiasis/bile duct stone, colon cancer/metastatic colon cancer/pneumothorax, cholelithiasis, metastatic lung cancer, cardiac failure congestive/pneumonia, arthritis bacterial, cerebral haemorrhage, coronary artery stenosis, intervertebral disc protrusion, diabetes mellitus, and renal infarct) and by 1.7% (2 of 120) of subjects in the 30 mg cohort (periodontitis and intraocular pressure increased). A causal relationship to the study drug could not be ruled out for metastatic lung cancer, colon cancer[12)]/metastatic colon cancer, arthritis bacterial, cerebral haemorrhage, and cardiac failure congestive/pneumonia in the 20 mg cohort, but the outcome was recovery for all of them except metastatic lung cancer and colon cancer/metastatic colon cancer.

Adverse events leading to discontinuation were reported by 15.7% (19 of 121) of subjects in the 20 mg cohort and 8.3% (10 of 120) of subjects in the 30 mg cohort. The main adverse events were psoriasis (5 subjects in the 20 mg cohort, 5 subjects in the 30 mg cohort) and diarrhoea (1 subject in the 20 mg cohort, 2 subjects in the 30 mg cohort).

Adverse drug reactions were reported by 28.1% (34 of 121) of subjects in the 20 mg cohort and 30.8% (37 of 120) of subjects in the 30 mg cohort.

11) A 52-year-old male subject with a smoking history of 34 years. Diagnosis of metastatic lung cancer was made 197 days after the start of the treatment with study drug, whereupon the study in this subject was discontinued. He died of the lung cancer 254 days after the start of the treatment. The attending physician determined that the causal relationship of the metastatic lung cancer to the study drug could not be ruled out.

12) A 66-year-old male subject was diagnosed with cancer of ascending colon and sigmoid colon on Day 276 of treatment, whereupon the study in this subject was discontinued on Day 279. Colorectomy was performed on Day 356 and metastasis to lymph nodes of the sigmoid colon was confirmed. Chemotherapy with tegafur/uracil was started from Day 450 and, as of Day 525, the colon cancer is healing, according to the opinion of the attending physician.

**Table 32. Adverse events reported by ≥3% of subjects receiving apremilast within 72 weeks of treatment (safety analysis population)**

| | 20 mg cohort (n = 121) | 30 mg cohort (n = 120) |
|---|---|---|
| Nasopharyngitis | 28 (23.1) | 35 (29.2) |
| Diarrhoea | 10 (8.3) | 12 (10.0) |
| Influenza | 6 (5.0) | 3 (2.5) |
| Psoriasis | 5 (4.1) | 5 (4.2) |
| Arthralgia | 5 (4.1) | 2 (1.7) |
| Contusion | 5 (4.1) | 2 (1.7) |
| Back pain | 4 (3.3) | 5 (4.2) |
| Insomnia | 4 (3.3) | 3 (2.5) |
| Hypertension | 4 (3.3) | 2 (1.7) |
| Abdominal discomfort | 3 (2.5) | 8 (6.7) |
| Arthropod bite | 3 (2.5) | 4 (3.3) |
| Folliculitis | 3 (2.5) | 5 (4.2) |
| Eczema | 2 (1.7) | 5 (4.2) |
| Urticaria | 2 (1.7) | 4 (3.3) |
| Dermatitis contact | 2 (1.7) | 5 (4.2) |
| Tinea pedis | 1 (0.8) | 5 (4.2) |
| Headache | 1 (0.8) | 5 (4.2) |
| Myalgia | 0 | 4 (3.3) |

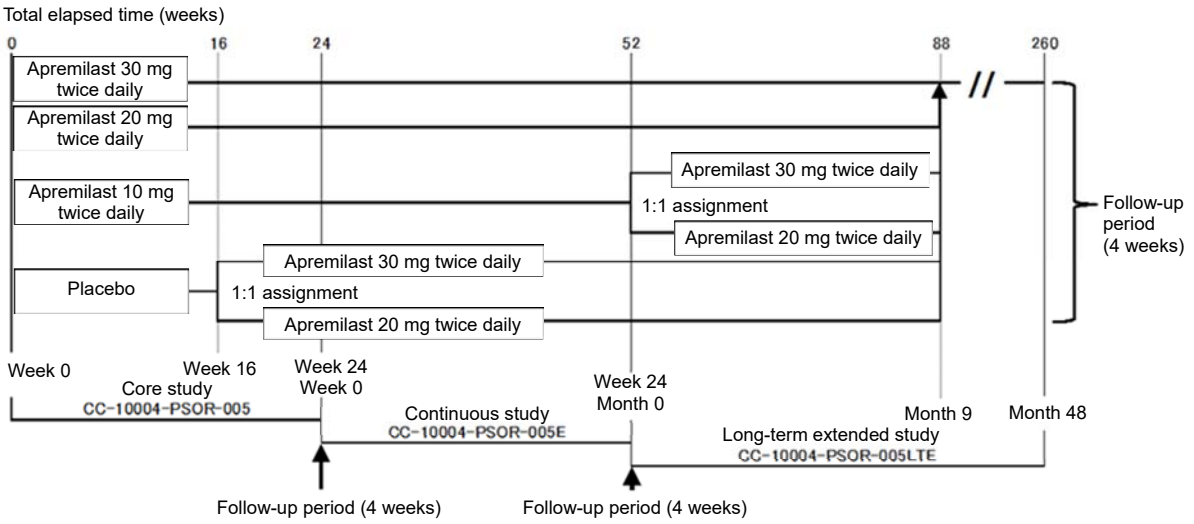
Number of subjects (%)

### 7.2.3 Foreign phase II study (CTD 5.3.5.1.2, Study CC-10004-PSOR-005-E-LTE [September 2008 to May 2015 (data cut-off, July 2011)]) (the study to be bridged)

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriasis vulgaris or psoriatic arthritis with moderate to severe plaque rash[13)] (target sample size, 348 subjects [87 per group]) in the US and Canada.

The study consisted of 3 parts (core study part comprising 16-week placebo-controlled period and 8-week active drug administration period, continuous treatment part from Week 24 to Week 52 of administration, long-term treatment part from Week 52 to 5 years at the maximum). The treatment was to be started by the gradual dose increase as shown in Table 33. Subjects were to receive apremilast 10, 20, or 30 mg, or placebo, as shown in Figure 3. Data obtained up to Week 88 of administration were submitted in the present application.

13) Subjects who met both of the following criteria: (a) PASI score ≥12 from ≥6 months before screening and the area of plaque rash ≥10% of the body surface area and (b) systemic therapy or phototherapy deemed necessary by the physician.




The primary assessment was to be performed at Week 16. Subjects in the placebo group were reassigned to the apremilast 20 or 30 mg group at Week 16.
At Week 52, subjects in the apremilast 10 mg group were reassigned to the apremilast 20 or 30 mg group.

**Figure 3. Dosage regimen and administration schedule in Study CC-10004-PSOR-005-E-LTE**

**Table 33. Schedule for gradual dose increase of apremilast in Study CC-10004-PSOR-005-E-LTE**

| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 and thereafter |
|---|---|---|---|---|---|
| Morning[a)] | 10 mg | 10 mg | 20 mg | 20 mg | 30 mg |
| Evening[a)] | 10 mg | 10 mg | 20 mg | 20 mg | 30 mg |

Subjects in the 10 mg group continued to receive 10 mg from Day 2 and subjects in the 20 mg group continued to receive 20 mg from Day 3.
a) The study drug was to be administered at intervals of approximately 12 hours without regard to meals.

All of the 352 randomized subjects (89 in the 10 mg group, 87 in the 20 mg group, 88 in the 30 mg group, and 88 in the placebo group) were included in the ITT population, and the ITT population was used for the efficacy analysis. Of subjects in the ITT population, all of subjects who received the study drug were included in the safety analysis population. During the placebo-controlled period, study discontinuation occurred in 11.2% (10 of 89) of subjects in the 10 mg group, 24.1% (21 of 87) of subjects in the 20 mg group, 20.5% (18 of 88) of subjects in the 30 mg group, and 18.2% (16 of 88) of subjects in the placebo group. The main reasons for the discontinuation included adverse events (1.1% [1 of 89] in the 10 mg group, 9.2% [8 of 87] in the 20 mg group, 11.4% [10 of 88] in the 30 mg group, 5.7% [5 of 88] in the placebo group) and inadequate response (3.4% [3 of 89] in the 10 mg group, 2.3% [2 of 87] in the 20 mg group, 2.3% [2 of 88] in the 30 mg group, 4.5% [4 of 88] in the placebo group). Of 287 subjects who completed the 16-week placebo-controlled period, 280 subjects (34 in the placebo/20 mg group, 36 in the placebo/30 mg group, 77 in the continuous 10 mg group, 66 in the continuous 20 mg group, and 67 in the continuous 30 mg group) continued the study. Of 253 subjects who completed the administration for 24 weeks, 209 subjects (27 in the placebo/20 mg group, 27 in the placebo/30 mg group, 47 in the continuous 10 mg group, 50 in the continuous 20 mg group, and 58 in the continuous 30 mg group) proceeded to the extended treatment part.

Table 34 shows the PASI 75 response rate at Week 16, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of the apremilast 20 and 30 mg groups. Table 34 also shows the PASI 50 and 90 response rates and the sPGA (0 or 1) response rate at Week 16, the secondary endpoints.

**Table 34. PASI 50, 75, 90 response rates and sPGA response rate at Week 16 of administration (ITT, LOCF)**

| | 10 mg | 20 mg | 30 mg | Placebo | Difference from placebo [95% CI] *P* value[a) b)] | | |
|---|---|---|---|---|---|---|---|
| | | | | | 10 mg | 20 mg | 30 mg |
| PASI 50 response rate | 38.2 (34/89) | 47.1 (41/87) | 60.2 (53/88) | 25.0 (22/88) | 13.2 [−0.4, 26.8] | 22.1 [8.3, 36.0] | 35.2 [21.6, 48.9] |
| PASI 75 response rate | 11.2 (10/89) | 28.7 (25/87) | 40.9 (36/88) | 5.7 (5/88) | 5.6 [−2.6, 13.7] *P* = 0.1846 | 23.1 [12.4, 33.7] *P* < 0.0001 | 35.2 [23.9, 46.6] *P* < 0.0001 |
| PASI 90 response rate | 4.5 (4/88) | 9.2 (8/87) | 11.4 (10/88) | 1.1 (1/88) | 3.4 [−1.5, 8.2] | 8.1 [1.6, 14.5] | 10.2 [3.2, 17.2] |
| sPGA (0 or 1) response rate[c)] | 10.5 (9/86) | 25.0 (20/80) | 33.7 (28/83) | 12.6 (11/87) | −2.2 [−11.7, 7.3] | 12.4 [0.6, 24.1] | 21.1 [8.8, 33.4] |

% (number of subjects)

a) Chi-square test

b) Adjusted for multiplicity by a fixed rank test with the rank defined in the order of paired comparison between the placebo group and the 20 mg group, the 30 mg group, and the 10 mg group

c) Analysis was performed in subjects with baseline sPGA score of ≥3.

During the placebo-controlled period, adverse events were reported by 66.3% (59 of 89) of subjects in the 10 mg group, 77.0% (67 of 87) of subjects in the 20 mg group, 81.8% (72 of 88) of subjects in the 30 mg group, and 64.8% (57 of 88) of subjects in the placebo group. Table 35 shows the main adverse events reported.

Death occurred in 1 subject in the placebo group (sudden death).

Serious adverse events were reported by 3.4% (3 of 87) of subjects in the 20 mg group (cellulitis, psoriasis, and nephrolithiasis), 4.5% (4 of 88) of subjects in the 30 mg group (pregnancy [2 subjects], prostate cancer, and myocardial infarction), and 2.3% (2 of 88) of subjects in the placebo group (drug eruption and sudden death). A causal relationship to the study drug was ruled out for all events.

Adverse events leading to discontinuation were reported by 2.2% (2 of 89) of subjects in the 10 mg group, 9.2% (8 of 87) of subjects in the 20 mg group, 13.6% (12 of 88) of subjects in the 30 mg group, and 5.7% (5 of 88) of subjects in the placebo group. The main event was nausea (3 subjects in the 20 mg group, 2 subjects in the 30 mg group).

Adverse drug reactions were reported by 22.5% (20 of 89) of subjects in the 10 mg group, 26.4% (23 of 87) of subjects in the 20 mg group, 36.4% (32 of 88) of subjects in the 30 mg group, and 12.5% (11 of 88) of subjects in the placebo group.

**Table 35. Adverse events reported by ≥3% of subjects in either of the apremilast groups during the placebo-controlled period (safety analysis population)**

| | 10 mg (n = 89) | 20 mg (n = 87) | 30 mg (n = 88) | Placebo (n = 88) |
|---|---|---|---|---|
| Nausea | 10 (11.2) | 13 (14.9) | 17( 19.3) | 7 (8.0) |
| Upper respiratory tract infection | 9 (10.1) | 11 (12.6) | 14 (15.9) | 4 (4.5) |
| Nasopharyngitis | 8 (9.0) | 7 (8.0) | 5 (5.7) | 7 (8.0) |
| Diarrhoea | 6 (6.7) | 6 ( 6.9) | 12 (13.6) | 4 (4.5) |
| Headache | 5 (5.6) | 8 (9.2) | 7 (8.0) | 5 (5.7) |
| Insomnia | 4 (4.5) | 1 (1.1) | 1 (1.1) | 0 |
| Tension headache | 3 (3.4) | 2 (2.3) | 14 (15.9) | 7 (8.0) |
| Sinusitis | 3 (3.4) | 0 | 3 (3.4) | 2 (2.3) |
| Viral upper respiratory tract infection | 2 (2.2) | 8 (9.2) | 7 (8.0) | 8 (9.1) |
| Lymphadenopathy | 2 (2.2) | 3 (3.4) | 1 (1.1) | 1 (1.1) |
| Fatigue | 2 (2.2) | 0 | 4 (4.5) | 3 (3.4) |
| Dyspepsia | 1 (1.1) | 5 (5.7) | 4 (4.5) | 2 (2.3) |
| Gastroenteritis | 1 (1.1) | 4 (4.6) | 5 (5.7) | 3 (3.4) |
| Excoriation | 1 (1.1) | 2 (2.3) | 3 (3.4) | 1 (1.1) |
| Arthralgia | 1 (1.1) | 3 (3.4) | 1 (1.1) | 1 (1.1) |
| Bronchitis | 1 (1.1) | 3 (3.4) | 1 (1.1) | 1 (1.1) |
| Sinus headache | 1 (1.1) | 0 | 3 (3.4) | 0 |
| Vomiting | 0 | 3 (3.4) | 4 (4.5) | 1 (1.1) |
| Red blood cell sedimentation rate | 0 | 3 (3.4) | 4 (4.5) | 0 |
| Myalgia | 0 | 3 (3.4) | 2 (2.3) | 0 |
| Psoriasis | 0 | 3 (3.4) | 0 | 1 (1.1) |
| Post-traumatic pain | 0 | 1 (1.1) | 3 (3.4) | 0 |
| Decreased appetite | 0 | 0 | 3 (3.4) | 1 (1.1) |

Number of subjects (%)

Within 88 weeks after the start of treatment, adverse events were reported by 75.3% (67 of 89) of subjects in the 10 mg cohort, 80.2% (97 of 121) of subjects in the 20 mg cohort, and 88.7% (110 of 124) of subjects in the 30 mg cohort. Table 36 shows the main events reported. No death occurred in subjects receiving apremilast.

Serious adverse events were reported by 1.1% (1 of 89) of subjects in the 10 mg cohort (muscle haemorrhage), 6.6% (8 of 121) of subjects in the 20 mg cohort (cellulitis, anxiety/angina pectoris, pancreatitis, psoriasis, musculoskeletal chest pain, nephrolithiasis, epididymitis, and compartment syndrome/meniscus lesion/tibia fracture), and 4.8% (6 of 124) of subjects in the 30 mg cohort (prostate cancer and pregnancy [2 subjects each], myocardial infarction and asthma [1 subject each]). A causal relationship to the study drug could not be ruled out only for epididymitis in the 20 mg group, and its outcome was recovery.

Adverse events leading to discontinuation were reported by 5.6% (5 of 89) of subjects in the 10 mg cohort, 9.1% (11 of 121) of subjects in the 20 mg cohort, and 12.1% (15 of 124) of subjects in the 30 mg cohort. The main adverse event was nausea (1 subject in the 10 mg cohort, 4 subjects in the 20 mg cohort, and 2 subjects in the 30 mg cohort).

Adverse drug reactions were reported by 25.8% (23 of 89) of subjects in the 10 mg cohort, 25.6% (31 of 121) of subjects in the 20 mg cohort, and 36.3% (45 of 124) of subjects in the 30 mg cohort.

**Table 36. Adverse events reported by ≥3% of subjects receiving apremilast within 88 weeks after the start of treatment (safety analysis population)**

| | 10 mg cohort (n = 89) | 20 mg cohort (n = 121) | 30 mg cohort (n = 124) |
|---|---|---|---|
| Upper respiratory tract infection | 14 (45.7) | 19 (15.7) | 24 (19.4) |
| Nausea | 12 (13.5) | 20 (16.5) | 28 (22.6) |
| Nasopharyngitis | 10 (11.2) | 9 (7.4) | 13 (10.5) |
| Viral upper respiratory tract infection | 7 (7.9) | 13 (10.7) | 12 (9.7) |
| Headache | 7 (7.9) | 13 (10.7) | 11 (8.9) |
| Diarrhoea | 7 (7.9) | 9 (7.4) | 16 (12.9) |
| Muscle strain | 5 (5.6) | 5 (4.1) | 7 (5.6) |
| Sinusitis | 5 (5.6) | 3 (2.5) | 6 (4.8) |
| Gastroenteritis | 4 (4.5) | 7 (5.8) | 7 (5.6) |
| Tension headache | 4 (4.5) | 4 (3.3) | 18 (14.5) |
| Lymphadenopathy | 4 (4.5) | 3 (2.5) | 2 (1.6) |
| Insomnia | 4 (4.5) | 1 (0.8) | 3 (2.4) |
| Arthralgia | 3 (3.4) | 6 (5.0) | 5 (4.0) |
| Back pain | 3 (3.4) | 3 (2.5) | 5 (4.0) |
| Oedema peripheral | 3 (3.4) | 3 (2.5) | 3 (2.4) |
| Joint sprain | 3 (3.4) | 2 (1.7) | 1 (0.8) |
| Thermal burn | 3 (3.4) | 1 (0.8) | 0 |
| Viral infection | 2 (2.2) | 5 (4.1) | 0 |
| Bronchitis | 2 (2.2) | 4 (3.3) | 1 (0.8) |
| Alanine aminotransferase increased | 2 (2.2) | 4 (3.3) | 1 (0.8) |
| Urinary tract infection | 2 (2.2) | 3 (2.5) | 4 (3.2) |
| Migraine | 2 (2.2) | 2 (1.7) | 5 (4.0) |
| Oropharyngeal pain | 2 (2.2) | 2 (1.7) | 4 (3.2) |
| Fatigue | 2 (2.2) | 1 (0.8) | 4 (3.2) |
| Vomiting | 1 (1.1) | 8 (6.6) | 5 (4.0) |
| Dyspepsia | 1 (1.1) | 6 (5.0) | 8 (6.5) |
| Myalgia | 1 (1.1) | 6 (5.0) | 2 (1.6) |
| Oral herpes | 1 (1.1) | 4 (3.3) | 1 (0.8) |
| Cough | 1 (1.1) | 3 (2.5) | 5 (4.0) |
| Rhinitis | 1 (1.1) | 1 (0.8) | 4 (3.2) |
| Red blood cell sedimentation rate increased | 0 | 4 (3.3) | 6 (4.8) |
| Influenza | 0 | 4 (3.3) | 5 (4.0) |
| Post-traumatic pain | 0 | 4 (3.3) | 4 (3.2) |
| Decreased appetite | 0 | 0 | 4 (3.2) |

Number of subjects (%)

**7.2.4 Foreign phase II study (CTD 5.3.5.1.7, Study CC-10004-PSA-001 [March 2007 to May 2009])**
A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriatic arthritis[14)] (target sample size, 204 subjects [68 per group]) in 5 countries including Germany and Canada.

The treatment was to be started with once daily administration of apremilast 10 mg from Day 1 to Day 3 and 20 mg from Day 4 to Day 7, followed by a 12-week multiple dose administration of apremilast 20 mg twice daily (20 mg BID), 40 mg once daily (40 mg QD), or placebo. From Week 12 on, subjects who had been assigned to the placebo group were to be reassigned to the apremilast 20 mg BID or 40 mg QD group, and subjects who had been assigned to either of the apremilast group were to be continuously treated with the same dosage regimen up to Week 24.

Of 204 randomized subjects (69 in the 20 mg BID group, 67 in the 40 mg QD group, 68 in the placebo group), all of subjects who received the study drug were included in the safety analysis. All of the randomized subjects were included in the ITT population,[15)] and the ITT population was used for efficacy analysis. Within 12 weeks after the start of administration, study discontinuation occurred in 20.3% (14 of 69) of subjects in the 20 mg BID group, 10.4% (7 of 67) of subjects in the 40 mg QD group, and 26.5% (18 of 68) of subjects in the placebo group. The main reasons for the discontinuation included Grade ≥2 adverse events (5.8% [4 of 67] in the 20 mg BID group, 4.5% [3 of 69] in the 40 mg

14) Subjects who met all of the following criteria: (a) Diagnostic criteria of Moll & Wright, (b) joint tenderness at ≥3 sites and joint swelling at ≥3 sites at screening and baseline, (c) rheumatoid factor ≤30 IU/mL
15) Subjects who were randomized and had one or more ACR items evaluated at baseline

QD group, 2.9% [2 of 68] in the placebo group) and inadequate response (2.9% [2 of 67] in the 20 mg BID group, 10.3% [7 of 68] in the placebo group). Of 165 subjects who completed the treatment with the study drug for 12 weeks, 126 subjects (40 in the 20 mg BID group, 46 in the 40 mg QD group, 40 in the placebo group) continued the administration at the same dose or were assigned to a new dosage regimen.

Table 37 shows American College of Rheumatology 20 responder index (ACR 20 response rate) at Week 12 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of the 20 mg BID group and the 40 mg QD group. Table 37 also shows American College of Rheumatology 50 and 70 responder index (ACR 50 and 70 response rates) at Week 12 of administration, the secondary endpoints.

**Table 37. ACR 20, 50, and 70 response rates at Week 12 of administration (ITT, LOCF)**

| | 20 mg BID | 40 mg QD | Placebo | Difference from placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg BID | 40 mg QD |
| ACR 20 response rate | 43.5 (30/69) | 35.8 (24/67) | 11.8 (8/68) | 31.7 [17.7, 45.7] $P < 0.001$ | 24.1 [10.3, 37.9] $P = 0.002$ |
| ACR 50 response rate | 17.4 (12/69) | 13.4 (9/67) | 2.9 (2/68) | | |
| ACR 70 response rate | 5.8 (4/69) | 7.5 (5/67) | 1.5 (1/68) | | |

% (number of subjects)
a) Two-sided chi-square test with continuous correction
b) Adjusted for multiplicity using Bonferroni's method

Within 12 weeks after the start of administration, adverse events were reported by 85.5% (59 of 69) of subjects in the 20 mg BID group, 86.6% (58 of 67) of subjects in the 40 mg QD group, and 80.9% (55 of 68) of subjects in the placebo group. Table 38 shows the main events reported. No death occurred.

Serious adverse events were reported by 5.8% (4 of 69) of subjects in the 20 mg BID group (sinus tachycardia, biliary colic/hyperbilirubinaemia, intervertebral disc degeneration, and pregnancy of partner) and 5.9% (4 of 68) of subjects in the placebo group (fall, nausea/vomiting, nausea/balance disorder, and arthralgia). A causal relationship to the study drug could not be ruled out for nausea in 1 subject of the placebo group, but its outcome was recovery.

Adverse events leading to discontinuation were reported by 14.5% (10 of 69) of subjects in the 20 mg BID group, 9.0% (6 of 67) of subjects in the 40 mg QD group, and 10.3% (7 of 68) of subjects in the placebo group. The main event was psoriatic arthropathy (4.3% [3 of 67] of subjects in the 20 mg BID group, 1.5% [1 of 69] in the 40 mg QD group, 5.9% [4 of 68] in the placebo group).

Adverse drug reactions were reported by 37.7% (26 of 69) of subjects in the 20 mg BID group, 40.3% (27 of 67) of subjects in the 40 mg QD group, and 38.2% (26 of 68) of subjects in the placebo group.

**Table 38. Adverse events reported by ≥3 subjects in either of the apremilast groups within 12 weeks of administration (safety analysis population)**

| | 20 mg BID (n = 69) | 40 mg QD (n = 67) | Placebo (n = 68) |
|---|---|---|---|
| Diarrhoea | 14 (20.3) | 18 (26.9) | 6 (8.8) |
| Headache | 13 (18.8) | 15 (22.4) | 11 (16.2) |
| Nausea | 12 (17.4) | 15 (22.4) | 12 (17.6) |
| Nasopharyngitis | 8 (11.6) | 8 (11.9) | 12 (17.6) |
| Abdominal pain upper | 7 (10.1) | 4 (6.0) | 3 (4.4) |
| Migraine | 6 (8.7) | 2 (3.0) | 0 |
| Fatigue | 5 (7.2) | 11 (16.4) | 6 (8.8) |
| Vomiting | 4 (5.8) | 4 (6.0) | 4 (5.9) |
| Dizziness | 3 (4.3) | 7 (10.4) | 3 (4.4) |
| Psoriatic arthropathy | 3 (4.3) | 2 (3.0) | 6 (8.8) |
| Abdominal pain | 3 (4.3) | 2 (3.0) | 1 (1.5) |
| Dyspepsia | 3 (4.3) | 1 (1.5) | 3 (4.4) |
| Vertigo | 3 (4.3) | 0 | 1 (1.5) |
| Pruritus | 2 (2.9) | 5 (7.5) | 1 (1.5) |
| Upper respiratory tract infection | 1 (1.4) | 4 (6.0) | 0 |
| Sinusitis | 1 (1.4) | 3 (4.5) | 1 (1.5) |
| Joint injury | 1 (1.4) | 3 (4.5) | 0 |
| Back pain | 1 (1.4) | 2 (3.0) | 4 (5.9) |
| Influenza | 0 | 3 (4.5) | 1 (1.5) |

Number of subjects (%)

During the period from Week 12 to Week 24, adverse events were reported by 72.5% (29 of 40) of subjects in the 20 mg BID group, 65.2% (30 of 46) of subjects in the 40 mg QD group, 55.0% (11 of 20) of subjects in the placebo/20 mg BID group, and 80.0% (16 of 20) of subjects in the placebo/40 mg QD group. Table 39 shows the main events reported. No death occurred.

Serious adverse events were reported by 7.5% (3 of 40) of subjects in the 20 mg BID group (oral neoplasm/neoplasm prostate, osteoarthritis/synovitis, and hypertensive heart disease), 4.3% (2 of 46) of subjects in the 40 mg QD group (squamous cell carcinoma of skin and Parkinson's disease), 5.0% (1 of 20) of subjects in the placebo/20 mg BID group (abdominal abscess/wound infection), and 5.0% (1 of 20) of subjects in the placebo/40 mg QD group (tibia fracture). A causal relationship to the study drug could not be ruled out for abdominal abscess in the placebo/20 mg BID group, but its outcome was recovery.

Adverse events leading to discontinuation were reported by 5.0% (2 of 40) of subjects in the 20 mg BID group, 6.5% (3 of 46) of subjects in the 40 mg QD group, and 15.0% (3 of 20) of subjects in the placebo/20 mg BID group.

Adverse drug reactions were reported by 20.0% (8 of 40) of subjects in the 20 mg BID group, 26.1% (12 of 46) of subjects in the 40 mg QD group, 20.0% (4 of 20) of subjects in the placebo/20 mg BID group, and 20.0% (4 of 20) of subjects in the placebo/40 mg QD group.

**Table 39. Adverse events reported by ≥3 subjects in either of the apremilast groups from Week 12 to 24 (safety analysis population)**

| | 20 mg BID (n = 40) | 40 mg QD (n = 46) | Placebo/20 mg BID (n = 20) | Placebo/40 mg QD (n = 20) |
|---|---|---|---|---|
| Nasopharyngitis | 7 (17.5) | 7 (15.2) | 3 (15.0) | 6 (30.0) |
| Headache | 5 (12.5) | 2 (4.3) | 1 (5.0) | 0 |
| Rhinitis | 3 (7.5) | 0 | 0 | 0 |
| Diarrhoea | 2 (5.0) | 3 (6.5) | 0 | 4 (20.0) |
| Nausea | 1 (2.5) | 4 (8.7) | 1 (5.0) | 5 (25.0) |

Number of subjects (%)

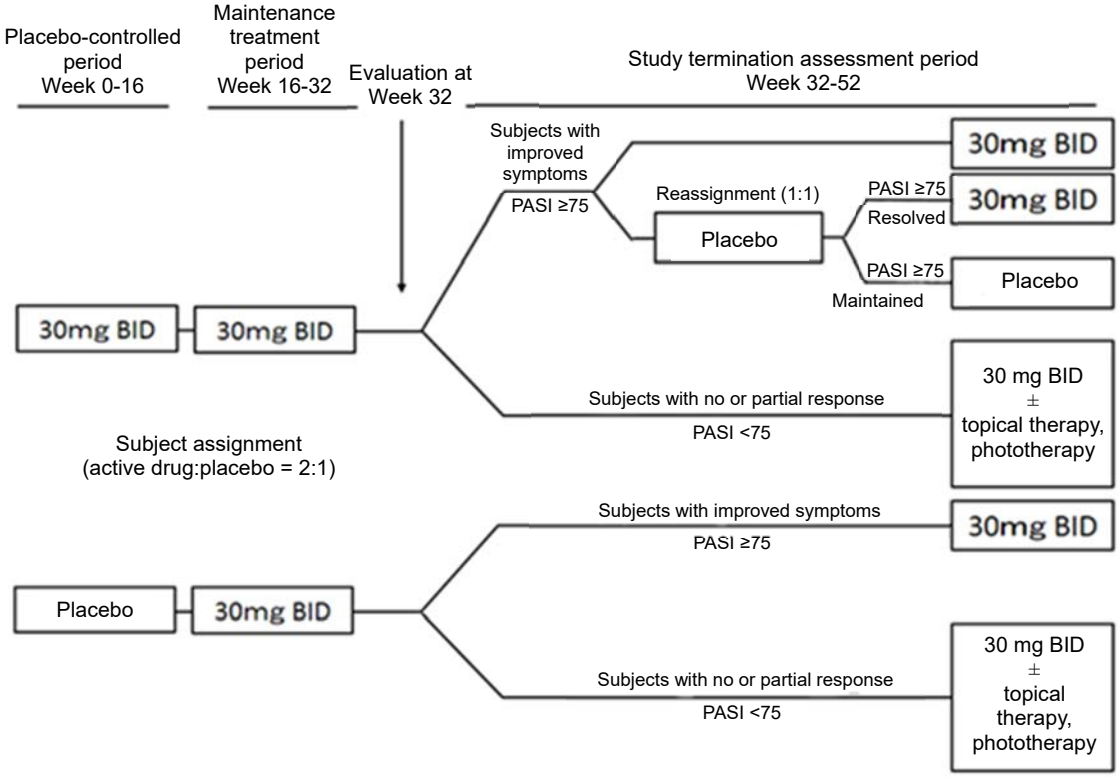
## 7.3 Phase III studies

### 7.3.1 Foreign phase III study (CTD 5.3.5.1.3, Study CC-10004-PSOR-008 [September 2010 – ongoing (data cut-off November 2011)])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriasis vulgaris or psoriatic arthritis

with moderate to severe plaque rash[16] (target sample size, 825 subjects [550 in the 30 mg group, 275 in the placebo group]) in 8 countries including the US and Canada.

The study consisted of 4 periods (placebo-controlled period from Week 0 to Week 16, maintenance treatment period from Week 16 to Week 32, study termination assessment period from Week 32 to Week 52, long-term safety assessment period from Week 52 to 5 years at the maximum). The treatment was to be started by the gradual dose increase as indicated in Table 29. Subjects were to receive apremilast 30 mg or placebo as shown in Figure 4. Data obtained up to Week 52 were submitted for the present application.




The primary endpoint was evaluated at Week 16, after which subjects in the placebo group received apremilast 30 mg.
Subjects in the apremilast groups who achieved PASI 75 at Week 32 were reassigned to the apremilast group or the placebo group.
Subjects who did not achieve PASI 75 at Week 32 were additionally treated with topical therapy and/or phototherapy at the discretion of the attending physician.
BID: Twice daily oral administration

**Figure 4. Dosage regimen and administration schedule in Study CC-10004-PSOR-008**

All of the 844 randomized subjects (562 in the 30 mg group, 282 in the placebo group) were included in full analysis set (FAS), and the FAS was used for the efficacy analysis. Of these, 842 subjects who received the study drug (560 in the 30 mg group, 282 in the placebo group) were included in the safety analysis population. During the placebo-controlled period, study discontinuation occurred in 10.5% (59 of 562) of subjects in the 30 mg group and 11.7% (33 of 282) of subjects in the placebo group. The main reasons for the discontinuation included adverse events (4.1% [23 of 562] in the 30 mg group, 1.8% [5 of 282] in the placebo group) and consent withdrawal (2.1% [12 of 562] in the 30 mg group, 3.2% [9 of 282] in the placebo group).

Of 752 subjects who completed the placebo-controlled period, 739 subjects (494 in the 30 mg/30 mg group, 245 in the placebo/30 mg group) proceeded to the maintenance treatment period and, of these, 607 subjects (399 in the 30 mg/30 mg group, 208 in the placebo/30 mg group) proceeded to the treatment termination assessment period. Of 399 subjects in the 30 mg/30 mg group, 154 subjects (77 in the 30 mg/30 mg/30 mg group, 77 in the 30 mg/30 mg/placebo group) who achieved ≥75% improvement in PASI were randomized and 245 subjects who failed to achieve ≥75% improvement in PASI were

[16] Subjects who met both of the following criteria: (a) PASI score ≥12, the area of plaque rash ≥10% of the body surface area, and sPGA score ≥3 at screening and baseline, and (b) systemic therapy or phototherapy deemed necessary by the physician.

continuously treated with apremilast 30 mg. Of 208 subjects who were in the placebo/30 mg group and enrolled in the treatment termination assessment period, 91 subjects who achieved ≥75% improvement in PASI were continuously treated with apremilast 30 mg, and 117 subjects who failed to achieve ≥75% improvement in PASI received topical therapy or phototherapy in addition to the continuous treatment with apremilast 30 mg.

Table 40 shows the PASI 75 response rate at Week 16 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and the 30 mg group, demonstrating the superiority of apremilast 30 mg to placebo. Table 40 also shows the PASI 50 and 90 response rates and the sPGA (0 or 1) response rate at Week 16 of administration, the secondary endpoints.

**Table 40. PASI 50, 75, and 90 response rates and sPGA response rate at Week 16 of administration (FAS, LOCF)**

| | 30 mg | Placebo | Difference from placebo [95% CI] *P* value[a)] |
|---|---|---|---|
| PASI 50 response rate | 58.7 (330/562) | 17.0 (48/282) | 41.7 [35.7, 47.7] |
| PASI 75 response rate | 33.1 (186/562) | 5.3 (15/282) | 27.8 [23.1, 32.5] *P* < 0.0001 |
| PASI 90 response rate | 9.8 (55/562) | 0.4 (1/282) | 9.4 [6.9, 12.0] |
| sPGA (0 or 1) response rate | 21.7 (122/562) | 3.9 (11/282) | 17.8 [13.7, 21.9] |

% (number of subjects)
a) Chi-square test

During the placebo-controlled period, adverse events were reported by 69.3% (388 of 560) of subjects in the 30 mg group and 55.7% (157 of 282) of subjects in the placebo group. Table 41 shows the main events reported.

Death occurred in 1 subject in the 30 mg group (cardiac failure[17)]) and in 1 subject in the placebo group (completed suicide[18)]). A causal relationship of cardiac failure to the study drug could not be ruled out.

Serious adverse events were reported by 2.1% (12 of 560) of subjects in the 30 mg group (pneumonia, microcytic anaemia/acute myocardial infarction, transient ischaemic attack, orthostatic hypotension, inguinal hernia/peripheral arterial occlusive disease, chronic obstructive pulmonary disease, abdominal pain/pyrexia, urticaria, heart rate increased, concussion, multiple injuries/road traffic accident, and cardiac failure), and in 2.8% (8 of 282) of subjects in the placebo group (inguinal hernia, Clostridium difficile colitis, anal cancer, completed suicide, cholecystitis/pneumonia/blood bilirubin increased, syncope, supraventricular tachycardia, and myocardial infarction). A causal relationship to the study drug could not be ruled out for cardiac failure, transient ischaemic attack, microcytic anaemia, and pneumonia in the 30 mg group.

Adverse events leading to discontinuation were reported by 5.2% (29 of 560) of subjects in the 30 mg group and 3.2% (9 of 282) of subjects in the placebo group. The main events were nausea (10 subjects in the 30 mg group, 1 subject in the placebo group), diarrhoea (7 subjects in the 30 mg group, 1 subject in the placebo group), headache (3 subjects in the 30 mg group), and dyspepsia (3 subjects in the 30 mg group).

Adverse drug reactions were reported by 40.0% (224 of 560) of subjects in the 30 mg group and 20.6% (58 of 282) of subjects in the placebo group.

17) A 30-year-old woman with risk factors for obesity. BMI 35.1 at screening. She was found dead on a bed at 111 days after treatment with apremilast 30 mg. Apremilast had been administered for 104 days. Autopsy showed pulmonary congestion and bilateral edema, findings consistent with acute cardiac failure, but did not reveal any other abnormalities.

18) A 28-year-old woman with past history of bipolar disorder, depression, insomnia, and suicide attempt. At 55 days after placebo administration, she committed suicide using a gun. The attending physician determined that the suicide had no causal relationship to the study drug.

**Table 41. Adverse events reported by ≥3% of subjects in the apremilast group during the placebo-controlled period (safety analysis population)**

| | 30 mg (n = 560) | Placebo (n = 282) |
|---|---|---|
| Diarrhoea | 105 (18.8) | 20 (7.1) |
| Nausea | 88 (15.7) | 19 (6.7) |
| Upper respiratory tract infection | 57 (10.2) | 21 (7.4) |
| Nasopharyngitis | 41 (7.3) | 23 (8.2) |
| Tension headache | 41 (7.3) | 12 (4.3) |
| Headache | 31 (5.5) | 13 (4.6) |
| Fatigue | 17 (3.0) | 3 (1.1) |
| Vomiting | 17 (3.0) | 2 (0.7) |
| Dyspepsia | 17 (3.0) | 1 (0.4) |

Number of subjects (%)

During the period up to Week 52 of administration, adverse events were reported by 78.7% (633 of 804) of subjects receiving apremilast. Table 42 shows the main events reported. No death occurred during the maintenance treatment period and the treatment termination assessment period.

Serious adverse events were reported by 4.2% (34 of 804) of subjects receiving apremilast. Serious adverse events reported by ≥3 subjects were coronary artery disease (0.4% [3 of 804 subjects]) and nephrolithiasis (0.4% [3 of 804 subjects]). After the end of apremilast administration, 1 subject was found to have rectal cancer[19)] for which a causal relationship to the study drug could not be ruled out.

Adverse events leading to discontinuation were reported by 7.3% (59 of 804) of subjects receiving apremilast. The main events were nausea (1.7% [14 of 804 subjects]), diarrhoea (1.2% [10 of 804 subjects]), psoriasis (0.7% [6 of 804 subjects]), vomiting (0.5% [4 of 804 subjects]), headache, tension headache, and dyspepsia (0.4% [3 of 804 subjects] each).

Adverse drug reactions were reported by 42.3% (340 of 804) of subjects receiving apremilast.

**Table 42. Adverse events reported by ≥3% of subjects receiving apremilast within 52 weeks after the start of treatment (safety analysis population)**

| | Subjects receiving apremilast (n = 804) |
|---|---|
| Diarrhoea | 150 (18.7) |
| Upper respiratory tract infection | 143 (17.8) |
| Nausea | 123 (15.3) |
| Nasopharyngitis | 108 (13.4) |
| Tension headache | 77 (9.6) |
| Headache | 52 (6.5) |
| Arthralgia | 37 (4.6) |
| Back pain | 36 (4.5) |
| Sinusitis | 36 (4.5) |
| Gastroenteritis | 33 (4.1) |
| Vomiting | 33 (4.1) |
| Hypertension | 32 (4.0) |
| Fatigue | 28 (3.5) |
| Migraine | 27 (3.4) |
| Cough | 26 (3.2) |
| Dyspepsia | 26 (3.2) |

Number of subjects (%)

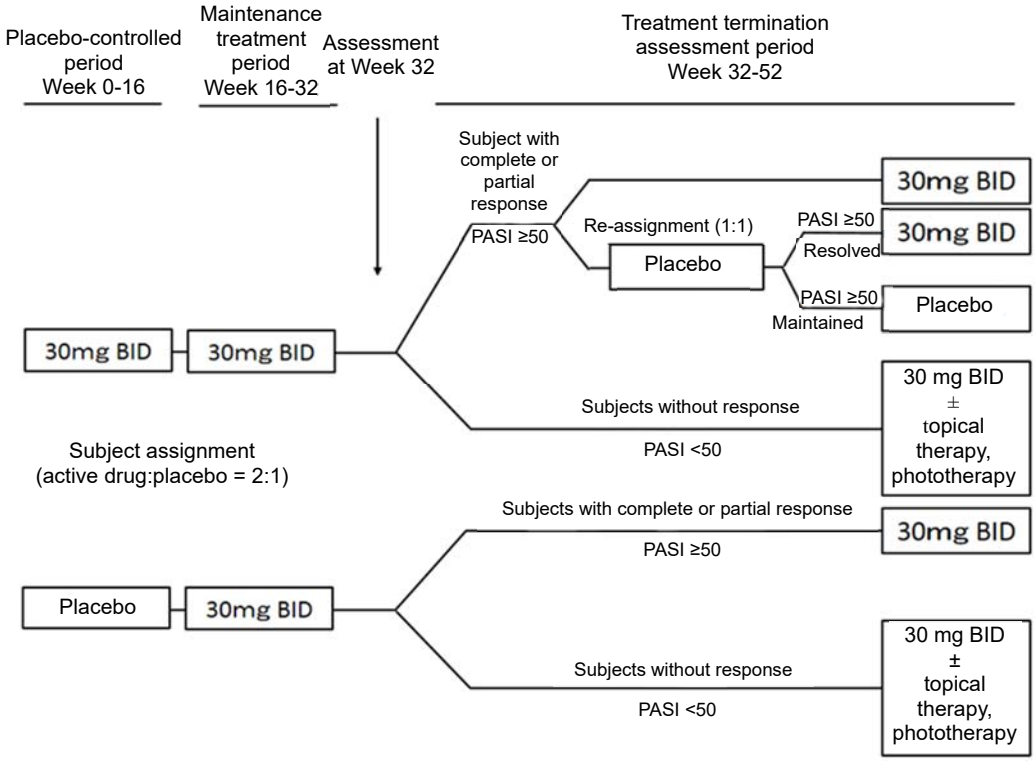
### 7.3.2 Foreign phase III study (CTD 5.3.5.1.4, Study CC-10004-PSOR-009 [November 2010 – ongoing (data cut-off, November 2011)])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriasis vulgaris or psoriatic arthritis

[19)] A 55-year-old man. The study drug was discontinued from Day 288 because of diarrhoea, bloody stool, and lower abdominal pain. Placebo was administered during the placebo-controlled period, after which apremilast 30 mg was administered for 142 days. At 34 days after the end of administration, the subject was diagnosed with rectal cancer by lower gastrointestinal endoscopy. The cancer was unresectable. Chemotherapy and radiation therapy were performed, but the subject has not recovered. The attending physician determined that rectal cancer was causally related to apremilast.

with moderate to severe plaque rash[20] (target sample size, 405 subjects [270 in the 30 mg group, 135 in the placebo group]) in 9 countries including the US and Canada.

The study consisted of 4 periods (placebo-controlled period from Week 0 to Week 16, maintenance treatment period from Week 16 to Week 32, treatment termination assessment period from Week 32 to Week 52, long-term safety assessment period from Week 52 to 5 years at the maximum). The treatment was to be started by the gradual dose increase as shown in Table 29. Subjects were to receive apremilast 30 mg or placebo as shown in Figure 5. Data obtained up to Week 52 were submitted for the present application.




The primary endpoint was evaluated at Week 16, after which subjects in the placebo group received apremilast 30 mg.
Subjects in the apremilast group who achieved PASI 50 at Week 32 were reassigned to the apremilast group or the placebo group.
Subjects who did not achieve PASI 50 at Week 32 were additionally treated with topical therapy and/or phototherapy at the discretion of the attending physician.
BID: Twice daily oral administration

**Figure 5. Dosage regimen and administration schedule in Study CC-10004-PSOR-009**

Of 413 randomized subjects (275 in the 30 mg group, 138 in the placebo group), 411 subjects (274 in the 30 mg group, 137 in the placebo group) excluding 2 with protocol deviation due to wrong assignment were included in FAS, and the FAS was used for the efficacy analysis. Of the subjects in the FAS, 408 subjects (272 in the 30 mg group, 136 in the placebo group) excluding 3 not treated with the study drug were included in the safety analysis population. During the placebo-controlled period, study discontinuation occurred in 12.7% (35 of 275) of subjects in the apremilast 30 mg group and 18.1% (25 of 138) of subjects in the placebo group. The main reasons for the discontinuation included adverse events (4.4% [12 of 275] in the 30 mg group, 5.8% [8 of 138] in the placebo group) and consent withdrawal (3.3% [9 of 275] in the 30 mg group, 5.1% [7 of 138] in the placebo group).

Of 351 subjects who completed the placebo-controlled period, 342 subjects (108 in the placebo/30 mg group, 234 in the 30 mg/30 mg group) proceeded to the maintenance treatment period and, of these, 277 subjects (96 in the placebo/30 mg group, 181 in the 30 mg/30 mg group) proceeded to the treatment

[20] Subjects who met both of the following criteria: (a) PASI score ≥12, the area of plaque rash ≥10% of the body surface area, and sPGA score ≥3 at screening and baseline, and (b) systemic therapy or phototherapy deemed necessary by the physician.

termination assessment period. Of 181 subjects in the 30 mg/30 mg group, 123 subjects who achieved ≥50% improvement in PASI were randomized (61 in the 30 mg/30 mg/30 mg group, 62 in the 30 mg/30 mg/placebo group), and 58 subjects who did not were continuously treated with apremilast 30 mg. Of 96 subjects who were in the placebo/30 mg group and enrolled in the treatment termination assessment period, 79 subjects who showed ≥50% improvement in PASI were continuously treated with apremilast 30 mg, and 17 subjects who showed <50% improvement in PASI were treated with topical therapy or phototherapy in addition to the continuous treatment with apremilast 30 mg.

Table 43 shows the PASI 75 response rate at Week 16 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and the 30 mg group, demonstrating the superiority of apremilast 30 mg to placebo. Table 43 also shows the PASI 50 and 90 response rates and the sPGA (0 or 1) response rate at Week 16 of administration, the secondary endpoints.

**Table 43. PASI 50, 75, and 90 response rates and sPGA response rate at Week 16 of administration (FAS, LOCF)**

| | 30 mg | Placebo | Difference from placebo [95% CI] *P* value[a)] |
|---|---|---|---|
| PASI 50 response rate | 55.5 (152/274) | 19.7 (27/137) | 35.8 [26.9, 44.7] |
| PASI 75 response rate | 28.8 (79/274) | 5.8 (8/137) | 23.0 [16.3, 29.6] *P* <0.0001 |
| PASI 90 response rate | 8.8 (24/274) | 1.5 (2/137) | 7.3 [3.4, 11.2] |
| sPGA (0 or 1) response rate | 20.4 (56/274) | 4.4 (6/137) | 16.1 [10.2, 21.9] |

% (number of subjects)
a) Chi-square test

During the placebo-controlled period, adverse events were reported by 68.0% (185 of 272) of subjects in the 30 mg group and 60.3% (82 of 136) of subjects in the placebo group. Table 44 shows the main events reported. No death occurred.

Serious adverse events were reported by 1.8% (5 of 272) of subjects in the 30 mg group (dysphagia, psoriatic arthropathy, gout, suicide attempt, and personality disorder/psoriasis/abdominal pain) and 2.2% (3 of 136) of subjects in the placebo group (syncope, palpitations, and non-cardiac chest pain). A causal relationship to the study drug was ruled out for all events.

Adverse events leading to discontinuation were reported by 5.5% (15 of 272) of subjects in the 30 mg group and 5.1% (7 of 136) of subjects in the placebo group. The main events were nausea (3 subjects in the 30 mg group), psoriasis (2 subjects in the 30 mg group, 3 subjects in the placebo group), and headache (2 subjects in the 30 mg group).

Adverse drug reactions were reported by 39.0% (106 of 272) of subjects in the 30 mg group and 21.3% (29 of 136) of subjects in the placebo group.

**Table 44. Adverse events reported by ≥3% of subjects in the apremilast group during the placebo-controlled period (safety analysis population)**

| | 30 mg (n = 272) | Placebo (n = 136) |
|---|---|---|
| Nausea | 50 (18.4) | 9 (6.6) |
| Diarrhoea | 43 (15.8) | 8 (5.9) |
| Nasopharyngitis | 20 (7.4) | 6 (4.4) |
| Tension headache | 20 (7.4) | 2 (1.5) |
| Headache | 17 (6.3) | 1 (0.7) |
| Vomiting | 14 (5.1) | 5 (3.7) |
| Upper respiratory tract infection | 13 (4.8) | 6 (4.4) |
| Abdominal pain | 9 (3.3) | 3 (2.2) |

Number of subjects (%)

Within 52 weeks after the start of administration, adverse events were reported by 77.9% (296 of 380) of subjects receiving apremilast. Table 45 shows the main events reported.

One subject died of haemorrhage intracranial[21)] during the treatment termination assessment period, but the causal relationship of the event to the study drug was ruled out.

Serious adverse events were reported by 4.7% (18 of 380) of subjects receiving apremilast. The main event was aggravated psoriasis in 0.5% (2 of 380) of the subjects.

Adverse events leading to discontinuation were reported by 7.1% (27 of 380) of subjects receiving apremilast. The main events reported were nausea and psoriasis in 0.8% (3 of 380) of subjects each and headache and weight decreased in 0.5% (2 of 380) of subjects each.

Adverse drug reactions were reported by 39.7% (151 of 380) of subjects receiving apremilast.

**Table 45. Adverse events reported by ≥3% of subjects receiving apremilast within 52 weeks after the start of treatment (safety analysis population)**

| | Subjects receiving apremilast (n = 380) |
|---|---|
| Nausea | 63 (16.6) |
| Diarrhoea | 55 (14.5) |
| Nasopharyngitis | 55 (14.5) |
| Upper respiratory tract infection | 35 (9.2) |
| Tension headache | 29 (7.6) |
| Vomiting | 24 (6.3) |
| Headache | 22 (5.8) |
| Back pain | 20 (5.3) |
| Urinary tract infection | 17 (4.5) |
| Dyspepsia | 16 (4.2) |
| Arthralgia | 15 (3.9) |
| Bronchitis | 14 (3.7) |
| Migraine | 13 (3.4) |
| Abdominal pain upper | 12 (3.2) |
| Psoriasis | 12 (3.2) |
| Pain in extremity | 12 (3.2) |

Number of subjects (%)

### 7.3.3 Foreign phase III study (CTD 5.3.5.1.5, Study CC-10004-PSOR-010 [October 2012 – ongoing (data cut-off July 2014)])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriasis vulgaris or psoriatic arthritis with moderate to severe plaque rash[22)] (target sample size, 240 subjects [80 per group]) in 11 countries including the US and the Czech Republic.

Subjects were to receive apremilast 30 mg twice daily (started by the gradual dose increase as shown in Table 31), etanercept (ETN; genetical recombination) 50 mg once every week, or placebo, for 16 weeks. From Week 16 on, all subjects were to be treated with apremilast 30 mg twice daily, and subjects deemed inadequately responsive by the investigator at Week 32 were allowed to receive topical therapy or phototherapy in addition. Data obtained up to Week 16 of administration were submitted for the present application.

Of 250 randomized subjects (83 in the 30 mg group, 83 in the ETN group, 84 in the placebo group), all of subjects who received the study drug were included in the safety analysis population. All randomized subjects were included in the mITT population,[23)] and the mITT population was used for the efficacy analysis. Within 16 weeks after the start of administration, study discontinuation occurred in 7.2% (6 of 83) of subjects in the 30 mg group, 2.4% (2 of 83) of subjects in the ETN group, and 10.7% (9 of 84) of

21) A 51-year-old woman. The subject received apremilast 30 mg up to Day 224, after which she received placebo. On Day 353, the subject was found unresponsive on the floor and transferred to a hospital, where she was diagnosed with brain death on Day 354. The attending physician determined that the death was not causally related to the study drug.

22) Subjects who met all of the following criteria: (a) PASI score ≥12, the area of plaque rash ≥10% of the body surface area, and sPGA score ≥3 at screening and baseline, (b) inadequately responsive, intolerant, or contraindicated to more than 1 type of conventional systemic therapies for psoriasis, (c) systemic therapy or phototherapy deemed necessary by the physician, and (d) no past history of treatment with biological products for psoriasis.

23) The population of subjects who met all of the following criteria: (a) Received the study drug, (b) baseline PASI score assessed, and (c) PASI score assessed after the study drug administration.

subjects in the placebo group. The main reason for the discontinuation included adverse events (2.4% [2 of 83] in the 30 mg group, 1.2% [1 of 83] in the ETN group, and 2.4% [2 of 84] in the placebo group).

Table 46 shows the PASI 75 response rate at Week 16 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and the 30 mg group, demonstrating the superiority of apremilast 30 mg to placebo. Table 46 also shows the PASI 50 and 90 response rates and the sPGA (0 or 1) response rate at Week 16 of administration, the secondary endpoints.

**Table 46. PASI 50, 75, and 90 response rates and sPGA response rate at Week 16 of administration (mITT, LOCF)**

| | 30 mg | ETN | Placebo | Difference between 30 mg and placebo [95% CI] *P* value[a)] | Difference between ETN and placebo [95% CI] *P* value[a) b)] |
|---|---|---|---|---|---|
| PASI 50 response rate | 62.7 (52/83) | 83.1 (69/83) | 33.3 (28/84) | 29.4 [14.9, 43.9] | 49.8 [36.9, 62.7] |
| PASI 75 response rate | 39.8 (33/83) | 48.2 (40/83) | 11.9 (10/84) | 27.5 [14.9, 40.1] *P* < 0.0001 | 35.9 [23.3, 48.5] *P* < 0.0001 |
| PASI 90 response rate | 14.5 (12/83) | 20.5 (17/83) | 3.6 (3/84) | 10.6 [2.0, 19.2] | 16.6 [7.2, 26.1] |
| sPGA (0 or 1) response rate[c)] | 21.7 (18/83) | 28.9 (24/83) | 3.6 (3/84) | 18.0 [8.4, 27.7] | 25.2 [14.8, 35.5] |

% (number of subjects)

a) Cochran-Mantel-Haenszel test stratified by BMI (≥30, <30)

b) Adjusted for multiplicity by a hierarchical procedure whereby the test was performed if a statistically significant result was obtained in the paired comparison between the placebo group and the apremilast group.

Within 16 weeks after the start of administration, adverse events were reported by 69.9% (58 of 83) of subjects in the 30 mg group, 53.0% (44 of 83) of subjects in the ETN group, and 59.5% (50 of 84) of subjects in the placebo group. Table 47 shows the main events reported. No death occurred.

Serious adverse events were reported by 3.6% (3 of 83) of subjects in the 30 mg group (pneumonia/sepsis, palpitations, and haematemesis) and 1.2% (1 of 83) of subjects in the ETN group (pneumonia/haemoptysis). A causal relationship to the study drug could not be ruled out for any of these serious adverse events except palpitations in the patient in the 30 mg group, but the outcome was recovery for all events.

Adverse events leading to discontinuation were reported by 3.6% (3 of 83) of subjects in the 30 mg group, 2.4% (2 of 83) of subjects in the ETN group, and 2.4% (2 of 84) of subjects in the placebo group. None of these events occurred in ≥2 subjects.

Adverse drug reactions were reported by 33.7% (28 of 83) of subjects in the 30 mg group, 25.3% (21 of 83) of subjects in the ETN group, and 26.2% (22 of 84) of subjects in the placebo group.

**Table 47. Adverse events reported by ≥3% of subjects in the apremilast group (safety analysis population)**

| | 30 mg (n = 83) | ETN (n =83) | Placebo (n = 84) |
|---|---|---|---|
| Headache | 11 (13.3) | 5 (6.0) | 5 (6.0) |
| Nausea | 9 (10.8) | 4 (4.8) | 2 (2.4) |
| Diarrhoea | 9 (10.8) | 1 (1.2) | 7 (8.3) |
| Upper respiratory tract infection | 6 (7.2) | 2 (2.4) | 2 (2.4) |
| Tension headache | 5 (6.0) | 3 (3.6) | 4 (4.8) |
| Nasopharyngitis | 4 (4.8) | 8 (9.6) | 8 (9.5) |
| Rhinitis | 4 (4.8) | 4 (4.8) | 1 (1.2) |
| Toothache | 4 (4.8) | 2 (2.4) | 2 (2.4) |
| Vomiting | 4 (4.8) | 2 (2.4) | 2 (2.4) |
| Oropharyngeal pain | 4 (4.8) | 1 (1.2) | 0 |
| Psoriatic arthropathy | 4 (4.8) | 0 | 2 (2.4) |
| Cough | 3 (3.6) | 4 (4.8) | 3 (3.6) |
| Back pain | 3 (3.6) | 3 (3.6) | 3 (3.6) |
| Arthralgia | 3 (3.6) | 3 (3.6) | 2 (2.4) |
| Pyrexia | 3 (3.6) | 2 (2.4) | 1 (1.2) |
| Urinary tract infection | 3 (3.6) | 0 | 2 (2.4) |

Number of subjects (%)

### 7.3.4 Foreign phase III study (CTD 5.3.5.1.8, Study CC-10004-PSA-002 [June 2010 – ongoing (data cut-off October 2012)])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriatic arthritis who have had an inadequate response to disease-modifying antirheumatic drugs (DMARD)[24] (target sample size, 495 subjects [165 per group]) in 13 countries including the US and Canada.

The treatment was to be started by the gradual dose increase as shown in Table 29. Subjects were to receive apremilast 20 or 30 mg or placebo twice daily for 24 weeks. Subjects in the placebo group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were reassigned under blinded conditions to either the 20 or 30 mg group, and subjects in the apremilast group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were continuously treated with apremilast at the same dose. From Week 24 on, subjects who had been assigned to the placebo group were reassigned to either the 20 or 30 mg group, and subjects who had been assigned to either of the apremilast groups were to be continuously treated with the same dosage regimen. Data obtained up to Week 52 of administration were submitted for the present application.

All of the 504 randomized subjects (168 in the 20 mg group, 168 in the 30 mg group, and 168 in the placebo group) were included in FAS, and the FAS was used for efficacy analysis. Of these, all subjects who received the study drug were included in the safety analysis set.

Within 24 weeks after the start of administration, study discontinuation occurred in 13.1% (22 of 168) of subjects in the apremilast 20 mg group, 11.9% (20 of 168) of subjects in the 30 mg group, and 10.7% (18 of 168) of subjects in the placebo group. Main reasons for the discontinuation included adverse events (4.8% [8 of 168] in the 20 mg group, 6.0% [10 of 168] in the 30 mg group, and 6.5% [11 of 168] in the placebo group) and inadequate response (3.0% [5 of 168] in the 20 mg group, 2.4% [4 of 168] in the 30 mg group, 2.4% [4 of 168] in the placebo group). Of 444 subjects who completed the administration for 24 weeks, 428 subjects (210 in the 20 mg group, 218 in the 30 mg group) continued to receive apremilast.

Table 48 shows the ACR 20 response rate at Week 16 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of 20 and 30 mg groups, demonstrating the superiority of apremilast 20 and 30 mg to placebo. Table 48 also shows ACR 50 and 70 response rates at Week 16 of administration, the secondary endpoints.

**Table 48. ACR 20, 50, and 70 response rates at Week 16 of administration (FAS, NRI)**

| | 20 mg | 30 mg | Placebo | Difference from the placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg group | 30 mg group |
| ACR 20 response rate | 30.4 (51/168) | 38.1 (64/168) | 19.0 (32/168) | 11.3 [2.2, 20.4] *P* = 0.0166 | 19.0 [9.7, 28.3] *P* = 0.0001 |
| ACR 50 response rate | 15.5 (26/168) | 16.1 (27/168) | 6.0 (10/168) | 9.5 [3.0, 16.0] | 10.3 [3.7, 16.8] |
| ACR 70 response rate | 6.0 (10/168) | 4.2 (7/168) | 1.2 (2/168) | 4.8 [0.8, 8.7] | 3.1 [-0.4, 6.5] |

% (number of subjects)
a) Cochran-Mantel-Haenszel test stratified by DMARD use (yes, no)
b) Adjusted for multiplicity using Hochberg's method

Within 24 weeks after the start of administration, adverse events were reported by 60.1% (101 of 168) of subjects in the 20 mg group, 61.3% (103 of 168) of subjects in the 30 mg group, and 48.2% (81 of 168) of subjects in the placebo group. Table 49 shows the main events reported.

One subject in the 20 mg group died of multi-organ failure, for which a causal relationship to the study drug was ruled out.

[24] Subjects who met both of the following criteria: (a) Subjects who met classification criteria for psoriatic arthritis (CASPAR) criteria at the screening and (b) subjects with joint tenderness at ≥3 sites and joint swelling at ≥3 sites after treatment with DMARD and at baseline

Serious adverse events were reported by 4.8% (8 of 168) of subjects in the 20 mg group (cardiac failure congestive, acute myocardial infarction, adnexa uteri cyst/endometriosis, carpal tunnel syndrome, cholelithiasis, depression, multi-organ failure,[25)] and suicide attempt), 5.4% (9 of 168) of subjects in the 30 mg group (arthritis, atrial fibrillation, breast cancer,[26)] cholecystitis acute, cholecystitis chronic, clostridial infection, deep vein thrombosis/hypotension, nausea/vomiting, and pneumonia), and 4.2% (7 of 168) of subjects in the placebo group (acute myocardial infarction/cardiac failure congestive/left ventricular dysfunction, angina pectoris/gastrointestinal haemorrhage, cellulitis, hypertensive crisis, prostate cancer, thinking abnormal, and wound infection bacterial). A causal relationship to the study drug could not be ruled out for clostridial infection, nausea/vomiting, and pneumonia in the 30 mg group and for thinking abnormal and hypertensive crisis in the placebo group. The outcomes of all these events were recovery.

Adverse events leading to discontinuation were reported by 6.0% (10 of 168) of subjects in the 20 mg group, 7.1% (12 of 168) of subjects in the 30 mg group, and 4.8% (8 of 168) of subjects in the placebo group. The main events reported included diarrhoea (2.4% [4 of 168] in the 30 mg group, 1.8% [3 of 168] in the placebo group) and nausea (1.2% [2 of 168] in the 20 mg group, 1.8% [3 of 168] in the 30 mg group, 1.2% [2 of 168] in the placebo group).

Adverse drug reactions were reported by 32.1% (54 of 168) of subjects in the 20 mg group, 41.7% (70 of 168) of subjects in the 30 mg group, and 19.0% (32 of 168) of subjects in the placebo group.

**Table 49. Adverse events reported by ≥3% of subjects in the apremilast groups within 24 weeks after the start of administration (safety analysis population)**

| | 20 mg (n = 168) | 30 mg (n = 168) | Placebo (n = 168)[a)] |
|---|---|---|---|
| Diarrhoea | 19 (11.3) | 32 (19.0) | 4 (2.4) |
| Headache | 17 (10.1) | 18 (10.7) | 8 (4.8) |
| Nausea | 16 (9.5) | 31 (18.5) | 11 (6.5) |
| Upper respiratory tract infection | 10 (6.0) | 7 (4.2) | 6 (3.6) |
| Nasopharyngitis | 6 (3.6) | 8 (4.8) | 5 (3.0) |
| Hypertension | 6 (3.6) | 2 (1.2) | 2 (1.2) |
| Decreased appetite | 5 (3.0) | 1 (0.6) | 1 (0.6) |
| Depression | 5 (3.0) | 1 (0.6) | 1 (0.6) |
| Dyspepsia | 4 (2.4) | 5 (3.0) | 4 (2.4) |
| Abdominal pain upper | 3 (1.8) | 7 (4.2) | 2 (1.2) |
| Vomiting | 2 (1.2) | 8 (4.8) | 1 (0.6) |
| Abdominal pain | 1 (0.6) | 8 (4.8) | 4 (2.4) |
| Gastrooesophageal reflux disease | 1 (0.6) | 5 (3.0) | 1 (0.6) |
| Migraine | 1 (0.6) | 5 (3.0) | 0 |

Number of subjects (%)

a) Includes events that occurred by Week 16 in subjects with early escape.

Within 52 weeks after the start of administration, adverse events were reported by 66.9% (164 of 245) of subjects in the 20 mg cohort and by 71.0% (174 of 245) of subjects in the 30 mg cohort. Table 50 shows the main events reported. No death occurred on or after Week 24.

Serious adverse events were reported by 5.7% (14 of 245) of subjects in the 20 mg cohort and 7.8% (19 of 245) of subjects in the 30 mg cohort. The event reported by ≥2 subjects in either 20 or 30 mg cohort was acute myocardial infarction (2 subjects in the 20 mg cohort), but a causal relationship to the study drug was ruled out for both cases.

Adverse events leading to discontinuation were reported by 6.5% (16 of 245) of subjects in the 20 mg cohort and 9.4% (23 of 245) of subjects in the 30 mg cohort. The main events reported included nausea

[25)] A 52-year-old woman with past history of obesity, chronic gastritis, and duodenitis. The subject experienced multi-organ failure from vitamin B12 deficiency anaemia, and died 73 days after the treatment with apremilast 30 mg. The investigator determined that the death was not causally related to apremilast.

[26)] A 58-year-old woman. A tumor in the right breast was found at a periodic medical checkup, 58 days after the treatment with apremilast 30 mg, whereupon the study in this subject was discontinued on Day 61. Right mastectomy was performed, and the event was judged as recovered. The investigator determined that the tumor was not causally related to the study drug.

(1.2% [3 of 245] in the 20 mg cohort, 1.6% [4 of 245] in the 30 mg cohort), diarrhoea (2.4% [6 of 245] in the 30 mg cohort), and headache (0.8% [2 of 245] in the 20 mg cohort, 1.6% [4 of 245] in the 30 mg cohort).

Adverse drug reactions were reported by 31.4% (77 of 245) of subjects in the 20 mg cohort and 44.1% (108 of 245) of subjects in the 30 mg cohort.

**Table 50. Adverse events reported by ≥3% of subjects in the 20 mg or 30 mg cohort within 52 weeks after the start of administration (safety analysis population)**

| | 20 mg cohort (n = 245) | 30 mg cohort (n = 245) |
|---|---|---|
| Diarrhoea | 27 (11.0) | 47 (19.2) |
| Nausea | 24 (9.8) | 35 (14.3) |
| Headache | 22 (9.0) | 24 (9.8) |
| Upper respiratory tract infection | 19 (7.8) | 14 (5.7) |
| Nasopharyngitis | 17 (6.9) | 16 (6.5) |
| Hypertension | 10 (4.1) | 9 (3.7) |
| Sinusitis | 10 (4.1) | 8 (3.3) |
| Gastrooesophageal reflux disease | 8 (3.3) | 10 (4.1) |
| Gastroenteritis | 8 (3.3) | 6 (2.4) |
| Abdominal pain | 6 (2.4) | 10 (4.1) |
| Dyspepsia | 5 (2.0) | 10 (4.1) |
| Abdominal pain upper | 5 (2.0) | 8 (3.3) |
| Arthralgia | 4 (1.6) | 8 (3.3) |
| Vomiting | 3 (1.2) | 10 (4.1) |

Number of subjects (%)

### 7.3.5 Foreign phase III study (CTD 5.3.5.1.9, Study CC-10004-PSA-003 [September 2010 – ongoing (data cut-off December 2012)])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriatic arthritis who have had an inadequate response to DMARD[27)] (target sample size, 495 subjects [165 per group]) in 16 countries including the Czech Republic and the US.

The treatment was to be started by the gradual dose increase as shown in Table 29. Subjects were to receive apremilast 20 or 30 mg or placebo twice daily for 24 weeks. Subjects in the placebo group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were reassigned under blinded conditions to either the 20 or 30 mg group, and subjects in the apremilast group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were continuously treated with apremilast at the same dose. From Week 24 on, subjects who had been assigned to the placebo group were reassigned to either the 20 or 30 mg group, and subjects who had been assigned to either of the apremilast groups were to be continuously treated with the same dosage regimen. Data obtained up to Week 52 of administration were submitted for the present application.

All of the 484 randomized subjects (163 in the 20 mg group, 162 in the 30 mg group, and 159 in the placebo group) were included in FAS, and the FAS was used for the efficacy analysis. All subjects who received the study drug were included in the safety analysis population.

Within 24 weeks after the start of administration, study discontinuation occurred in 12.3% (20 of 163) of subjects in the 20 mg group, 12.3% (20 of 162) of subjects in the 30 mg group, and 10.1% (16 of 159) of subjects in the placebo group. The main reasons for the discontinuation included inadequate response (1.8% [3 of 163] in the 20 mg group, 3.1% [5 of 162] in the 30 mg group) and consent withdrawal (1.2% [2 of 163] in the 20 mg group, 1.9% [3 of 162] in the 30 mg group, 1.3% [2 of 159] in the placebo group). Of 428 subjects who completed the administration for 24 weeks, 410 subjects (207 in the 20 mg group, 203 in the 30 mg group) continued to receive apremilast.

27) Subjects who met both of the following criteria: (a) Subjects who met CASPAR criteria at the screening and (b) subjects with joint tenderness at ≥3 sites and joint swelling at ≥3 sites despite treatment with DMARD

Table 51 shows the ACR 20 response rate at Week 16 of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of 20 and 30 mg groups, demonstrating the superiority of apremilast 20 and 30 mg to placebo. Table 51 also shows ACR 50 and 70 response rates at Week 16 of administration, the secondary endpoints.

**Table 51. ACR 20, 50, and 70 response rates at Week 16 of administration (FAS, NRI)**

| | 20 mg | 30 mg | Placebo | Difference from the placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg | 30 mg |
| ACR 20 response rate | 37.4 (61/163) | 32.1 (52/162) | 18.9 (30/159) | 18.7 [9.1, 28.2] *P* = 0.0002 | 13.4 [4.0, 22.7] *P* = 0.0060 |
| ACR 50 response rate | 14.7 (24/163) | 10.5 (17/162) | 5.0 (8/159) | 9.8 [3.4, 16.1] | 5.6 [−0.2, 11.3] |
| ACR 70 response rate | 3.7 (6/163) | 1.2 (2/162) | 0.6 (1/159) | 3.1 [0.0, 6.2] | 0.6 [−1.5, 2.7] |

% (number of subjects)
a) Cochran-Mantel-Haenszel test stratified by DMARD use (yes, no)
b) Adjusted for multiplicity using Hochberg's method

Within 24 weeks after the start of administration, adverse events were reported by 65.0% (106 of 163) of subjects in the 20 mg group, 59.3% (96 of 162) of subjects in the 30 mg group, and 45.3% (72 of 159) of subjects in the placebo group. Table 52 shows the main events reported. No death occurred.

Serious adverse events were reported by 3.7% (6 of 163) of subjects in the 20 mg group (anxiety/depression/palpitations/hyperhidrosis, diarrhoea, gastritis, myocardial ischaemia, ovarian cyst, and vertigo), 2.5% (4 of 162) of subjects in the 30 mg group (headache/hypertension, dysfunctional uterine bleeding, intervertebral disc disorder/tension headache/hypertensive heart disease, and tendon injury), and 1.9% (3 of 159) of subjects in the placebo group (diabetic neuropathy, intervertebral disc protrusion, and limb injury). A causal relationship to the study drug could not be ruled out for anxiety/depression/palpitations/hyperhidrosis, diarrhoea, and gastritis in the 20 mg group and headache in the 30 mg group, but the outcome was recovery for all of them.

Adverse events leading to discontinuation were reported by 3.1% (5 of 163) of subjects in the 20 mg group, 7.4% (12 of 162) of subjects in the 30 mg group, and 1.9% (3 of 159) of subjects in the placebo group. The main events reported were nausea (1.2% [2 of 163] in the 20 mg group, 3.1% [5 of 162] in the 30 mg group), diarrhoea (0.6% [1 of 163] in the 20 mg group, 2.5% [4 of 162] in the 30 mg group), and headache (2.5% [4 of 162] in the 30 mg group, 0.6% [1 of 159] in the placebo group).

Adverse drug reactions were reported by 32.5% (53 of 163) of subjects in the 20 mg group, 35.2% (57 of 162) of subjects in the 30 mg group, and 17.6% (28 of 159) of subjects in the placebo group.

**Table 52. Adverse events reported by ≥3% of subjects in either of the apremilast groups within 24 weeks after the start of administration (safety analysis population)**

| | 20 mg (n = 163) | 30 mg (n = 162) | Placebo (n = 159) [a)] |
|---|---|---|---|
| Nausea | 15 (9.2) | 26 (16.0) | 3 (1.9) |
| Diarrhoea | 18 (11.0) | 24 (14.8) | 8 (5.0) |
| Headache | 9 (5.5) | 19 (11.7) | 7 (4.4) |
| Upper respiratory tract infection | 14 (8.6) | 11 (6.8) | 6 (3.8) |
| Nasopharyngitis | 8 (4.9) | 8 (4.9) | 6 (3.8) |
| Vomiting | 5 (3.1) | 6 (3.7) | 2 (1.3) |
| Bronchitis | 5 (3.1) | 6 (3.7) | 0 |
| Abdominal pain upper | 4 (2.5) | 5 (3.1) | 0 |
| Dyspepsia | 4 (2.5) | 5 (3.1) | 1 (0.6) |
| Back pain | 5 (3.1) | 3 (1.9) | 0 |
| Decreased appetite | 5 (3.1) | 0 | 0 |
| Hypertension | 4 (2.5) | 5 (3.1) | 7 (4.4) |
| Fatigue | 5 (3.1) | 1 (0.6) | 0 |

Number of subjects (%)
a) Includes events that occurred by Week 16 in subjects with early escape.

Within 52 weeks after the start of administration, adverse events were reported by 67.9% (159 of 234) of subjects in the 20 mg cohort and 69.7% (163 of 234) of subjects in the 30 mg cohort. Table 53 shows the main events reported. No death occurred on or after Week 24.

Serious adverse events were reported by 4.7% (11 of 234) of subjects in the 20 mg cohort and 5.1% (12 of 234) of subjects in the 30 mg cohort. There were no events reported by ≥2 subjects in the 20 mg cohort or by ≥2 subjects in the 30 mg cohort.

Adverse events leading to discontinuation were reported by 5.1% (12 of 234) of subjects in the 20 mg cohort and 8.1% (19 of 234) of subjects in the 30 mg cohort.

Adverse drug reactions were reported by 32.9% (77 of 234) of subjects in the 20 mg cohort and 31.2% (73 of 234) of subjects in the 30 mg cohort.

**Table 53. Adverse events reported by ≥3% of subjects in either of apremilast cohorts within 52 weeks after the start of administration**

| | 20 mg cohort (n = 234) | 30 mg cohort (n = 234) |
|---|---|---|
| Diarrhoea | 26 (11.1) | 32 (13.7) |
| Upper respiratory tract infection | 26 (11.1) | 22 (9.4) |
| Nausea | 20 (8.5) | 32 (13.7) |
| Nasopharyngitis | 16 (6.8) | 10 (4.3) |
| Headache | 13 (5.6) | 23 (9.8) |
| Back pain | 11 (4.7) | 4 (1.7) |
| Hypertension | 10 (4.3) | 13 (5.6) |
| Sinusitis | 9 (3.8) | 7 (3.0) |
| Abdominal pain upper | 8 (3.4) | 7 (3.0) |
| Vomiting | 7 (3.0) | 10 (4.3) |
| Cough | 7 (3.0) | 6 (2.6) |
| Influenza | 7 (3.0) | 4 (1.7) |
| Decreased appetite | 7 (3.0) | 0 |
| Bronchitis | 6 (2.6) | 11 (4.7) |
| Dyspepsia | 5 (2.1) | 9 (3.8) |

Number of subjects (%)

### 7.3.6 Foreign phase III study (CTD 5.3.5.1.10, Study CC-10004-PSA-004 [September 2010 – ongoing (data cut-off March 2013)])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriatic arthritis who have had an inadequate response to DMARD[28)] (target sample size, 495 subjects [165 per group]) in 16 countries including the US and Poland.

The treatment was to be started by the gradual dose increase as shown in Table 29. Subjects were to receive apremilast 20 or 30 mg or placebo twice daily for 24 weeks. Subjects in the placebo group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were reassigned under blinded conditions to either the 20 or 30 mg group, and subjects in the apremilast group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were continuously treated with apremilast at the same dose. From Week 24 on, subjects who had been assigned to the placebo group were reassigned to either the 20 or 30 mg group, and subjects who had been assigned to either of the apremilast groups were to be continuously treated with the same dosage regimen. Data obtained up to Week 52 of administration were submitted for the present application.

All of the 505 randomized subjects (169 in the 20 mg group, 167 in the 30 mg group, and 169 in the placebo group) were included in FAS, and the FAS was used for the efficacy analysis. All subjects who

28) Subjects who met all of the following criteria: (a) Subjects who met CASPAR criteria at the screening, (b) subjects with joint tenderness at ≥3 sites and joint swelling at ≥3 sites despite treatment with DMARD, and (c) subjects with ≥1 plaque rash with ≥2 cm in size.

received the study drug were included in the safety analysis population[29] (170 in the 20 mg group, 167 in the 30 mg group, and 168 in the placebo group).

Within 24 weeks after the start of administration, study discontinuation occurred in 13.0% (22 of 169) of subjects in the apremilast 20 mg group, 13.2% (22 of 167) of subjects in the 30 mg group, and 13.6% (23 of 169) of subjects in the placebo group. The main reasons for the discontinuation included adverse events (7.1% [12 of 169] in the 20 mg group, 4.8% [8 of 167] in the 30 mg group, 5.9% [10 of 169] in the placebo group) and inadequate response (3.0% [5 of 169] in the 20 mg group, 4.2% [7 of 167] in the 30 mg group, 3.6% [6 of 169] in the placebo group). Of 438 subjects who completed the administration for 24 weeks, 417 subjects (207 in the 20 mg group, 210 in the 30 mg group) continued to receive apremilast.

Table 54 shows the ACR 20 response rate at Week 16, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of 20 and 30 mg groups, demonstrating the superiority of apremilast 20 and 30 mg to placebo. Table 54 also shows ACR 50 and 70 response rates at Week 16 of administration, the secondary endpoints.

**Table 54. ACR 20, 50, and 70 response rates at Week 16 of administration (FAS, NRI)**

| | 20 mg | 30 mg | Placebo | Difference from the placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg | 30 mg |
| ACR 20 response rate | 28.4 (48/169) | 40.7 (68/167) | 18.3 (31/169) | 9.8 [1.1, 18.6] *P* = 0.0295 | 22.3 [13.0, 31.6] *P* < 0.0001 |
| ACR 50 response rate | 12.4 (21/169) | 15.0 (25/167) | 8.3 (14/169) | 4.2 [-2.2, 10.6] | 6.8 [0.0, 13.5] |
| ACR 70 response rate | 4.7 (8/169) | 3.6 (6/167) | 2.4 (4/169) | 2.3 [-1.5, 6.2] | 1.2 [-2.4, 4.8] |

% (number of subjects)
a) Cochran-Mantel-Haenszel test stratified by DMARD use (yes, no)
b) Adjusted for multiplicity using Hochberg's method

Within 24 weeks after the start of administration, adverse events were reported by 58.8% (100 of 170) of subjects in the 20 mg group, 62.3% (104 of 167) of subjects in the 30 mg group, and 49.4% (83 of 168) of subjects in the placebo group. Table 55 shows the main events reported. No death occurred.

Serious adverse events were reported by 1.8% (3 of 169) of subjects in the 20 mg group (breast cancer, psoriatic arthropathy, and suicidal ideation), 3.6% (6 of 167) of subjects in the 30 mg group (atrial fibrillation, cholelithiasis, contusion/whiplash injury, intracranial aneurysm, lobar pneumonia, psoriatic arthropathy), and 5.4% (9 of 169) of subjects in the placebo group (pancreatitis acute and psoriatic arthropathy [2 subjects each], angioedema/urticaria, ankle fracture, cholelithiasis, hypertensive crisis, and tibia fracture [1 subject each]). A causal relationship to the study drug was ruled out for all events.

Adverse events leading to discontinuation were reported by 7.6% (13 of 170) of subjects in the 20 mg group, 7.2% (12 of 167) of subjects in the 30 mg group, and 6.0% (10 of 168) of subjects in the placebo group. The main events were nausea (1.8% [3 of 170] in the 20 mg group, 3.0% [5 of 167] in the 30 mg group, 0.6% [1 of 168] in the placebo group) and diarrhoea (2.4% [4 of 170] in the 20 mg group, 1.8% [3 of 167] in the 30 mg group).

Adverse drug reactions were reported by 29.4% (50 of 170) of subjects in the 20 mg group, 37.1% (62 of 167) of subjects in the 30 mg group, and 19.6% (33 of 168) of subjects in the placebo group.

[29] Due to an error in study drug administration, the number of randomized subjects is not identical with the number of subjects in the safety analysis population.

**Table 55. Adverse events reported by ≥3% of subjects in either of the apremilast groups within 24 weeks after the start of administration (safety analysis population)**

| | 20 mg (n = 170) | 30 mg (n = 167) | Placebo (n = 168)[a)] |
|---|---|---|---|
| Diarrhoea | 26 (15.3) | 26 (15.6) | 3 (1.8) |
| Nausea | 19 (11.2) | 23 (13.8) | 9 (5.4) |
| Headache | 16 (9.4) | 20 (12.0) | 8 (4.8) |
| Upper respiratory tract infection | 11 (6.5) | 12 (7.2) | 3 (1.8) |
| Nasopharyngitis | 7 (4.1) | 4 (2.4) | 2 (1.2) |
| Vomiting | 5 (2.9) | 8 (4.8) | 1 (0.6) |
| Cough | 4 (2.4) | 5 (3.0) | 0 |
| Fatigue | 3 (1.8) | 8 (4.8) | 2 (1.2) |
| Frequent bowel movements | 2 (1.2) | 7 (4.2) | 0 |
| Urinary tract infection | 2 (1.2) | 5 (3.0) | 1 (0.6) |

Number of subjects (%)

a) Includes events that occurred by Week 16 in subjects with early escape.

Within 52 weeks after the start of administration, adverse events were reported by 66.4% (160 of 241) of subjects in the 20 mg cohort and 68.2% (165 of 242) of subjects in the 30 mg cohort. Table 56 shows the main events reported. No death occurred.

Serious adverse events were reported by 5.4% (13 of 241) of subjects in the 20 mg cohort and 4.1% (10 of 242) of subjects in the 30 mg cohort. The event reported by ≥2 subjects in any dose cohort was psoriatic arthropathy (2 subjects in the 20 mg cohort, 1 subject in the 30 mg cohort).

Adverse events leading to discontinuation were reported by 9.1% (22 of 241) of subjects in the 20 mg cohort and 5.8% (14 of 242) of subjects in the 30 mg cohort. The main events reported were nausea (1.2% [3 of 241] in the 20 mg cohort, 2.5% [6 of 242] in the 30 mg cohort) and diarrhoea (1.7% [4 of 241] in the 20 mg cohort, 1.7% [4 of 242] in the 30 mg cohort).

Adverse drug reactions were reported by 33.2% (80 of 241) of subjects in the 20 mg cohort and 35.1% (85 of 242) of subjects in the 30 mg cohort.

**Table 56. Adverse events reported by ≥3% of subjects in either of apremilast cohorts within 52 weeks after the start of administration (safety analysis population)**

| | 20 mg cohort (n = 241) | 30 mg cohort (n = 242) |
|---|---|---|
| Diarrhoea | 32 (13.3) | 33 (13.6) |
| Headache | 26 (10.8) | 26 (10.7) |
| Nausea | 24 (10.0) | 36 (14.9) |
| Upper respiratory tract infection | 21 (8.7) | 20 (8.3) |
| Nasopharyngitis | 12 (5.0) | 10 (4.1) |
| Abdominal pain upper | 9 (3.7) | 5 (2.1) |
| Vomiting | 8 (3.3) | 12 (5.0) |
| Urinary tract infection | 8 (3.3) | 8 (3.3) |
| Hypertension | 8 (3.3) | 8 (3.3) |
| Sinusitis | 7 (2.9) | 9 (3.7) |
| Dizziness | 5 (2.1) | 9 (3.7) |
| Arthralgia | 4 (1.7) | 11 (4.5) |
| Fatigue | 4 (1.7) | 10 (4.1) |
| Frequent bowel movements | 2 (0.8) | 9 (3.7) |

Number of subjects (%)

### 7.3.7 Foreign phase III study (CTD 5.3.5.1.11, Study CC-10004-PSA-005 [December 2010 – ongoing (data cut-off January 2013)])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of apremilast in patients with psoriatic arthritis without history of treatment with DMARD[30)] (target sample size, 495 subjects [165 per group]) in 15 countries including Russia and the US.

30) Subjects who met all of the following criteria: (a) Subjects who met CASPAR criteria at the screening, (b) subjects with joint tenderness at ≥3 sites and joint swelling at ≥3 sites, and (c) subjects without history of treatment with DMARD.

The treatment was to be started by the gradual dose increase as shown in Table 29. Subjects were to receive apremilast 20 or 30 mg or placebo twice daily for 24 weeks. Subjects in the placebo group who did not show ≥20% improvement in swollen or tender joint count at Week 16 after the start of administration were to be reassigned under blinded conditions to either the 20 or 30 mg group. From Week 24 on, subjects who had been assigned to the placebo group were reassigned to either the 20 or 30 mg group, and subjects who had been assigned to either of the apremilast groups were to be continuously treated with the same dosage regimen. Data obtained up to Week 24 of administration were submitted for the present application.

Of 528 randomized subjects, 527 subjects were included in FAS (175 in the 20 mg group, 176 in the 30 mg group, 176 in the placebo group) excluding 1 misassigned subject, and the FAS was used for the efficacy analysis. Of these, 526 subjects (175 in the 20 mg group, 175 in the 30 mg group, and 176 in the placebo group) except 1 not receiving the study drug were included in the safety analysis population.

Within 24 weeks after the start of administration, study discontinuation occurred in 8.6% (15 of 175) of subjects in the apremilast 20 mg group, 11.9% (21 of 176) of subjects in the 30 mg group, and 11.4% (20 of 176) of subjects in the placebo group. The main reasons for the discontinuation included consent withdrawal (2.3% [4 of 175] in the 20 mg group, 5.7% [10 of 176] in the 30 mg group, 4.5% [8 of 176] in the placebo group) and adverse events (2.3% [4 of 175] in the 20 mg group, 3.4% [6 of 176] in the 30 mg group, 2.3% [4 of 176] in the placebo group).

Table 57 shows the ACR 20 response rate at Week 16, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison of the endpoint between the placebo group and each of the 20 and 30 mg groups, demonstrating the superiority of apremilast 20 and 30 mg to placebo. Table 57 also shows ACR 50 and 70 response rates at Week 16 of administration, the secondary endpoints.

**Table 57. ACR 20, 50, and 70 response rates at Week 16 of administration (FAS, NRI)**

| | 20 mg | 30 mg | Placebo | Difference from the placebo [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|
| | | | | 20 mg | 30 mg |
| ACR 20 response rate | 28.0 (49/175) | 30.7 (54/176) | 15.9 (28/176) | 12.1 [3.5, 20.7] *P* = 0.0062 | 14.8 [6.1, 23.5] *P* = 0.0010 |
| ACR 50 response rate | 11.4 (20/175) | 11.4 (20/176) | 4.5 (8/176) | 6.9 [1.3, 12.5] | 6.8 [1.2, 12.4] |
| ACR 70 response rate | 4.0 (7/175) | 4.0 (7/175) | 1.1 (2/176) | 2.9 [−0.4, 6.2] | 2.8 [−0.4, 6.1] |

% (number of subjects)
a) Chi-square test
b) Adjusted for multiplicity using Hochberg's method

Within 24 weeks after the start of administration, adverse events were reported by 49.7% (87 of 175) of subjects in the 20 mg group, 56.6% (99 of 175) of subjects in the 30 mg group, and 41.5% (73 of 176) of subjects in the placebo group. Table 58 shows the main events reported. No death occurred.

Serious adverse events were reported by 1.7% (3 of 175) of subjects in the 20 mg group (chronic tonsillitis/papilloma, epilepsy/confusional state/arthralgia/back pain/sciatica, and road traffic accident/multiple injuries), 0.6% (1 of 175) of subjects in the 30 mg group (pyelonephritis acute), and 2.8% (5 of 176) of subjects in the placebo group (diabetic gangrene, haemoptysis, psoriatic arthropathy, endometrial hyperplasia, and incisional hernia). A causal relationship to apremilast could not be ruled out for pyelonephritis acute in the 30 mg group, but the outcome was recovery.

Adverse events leading to discontinuation were reported by 2.3% (4 of 175) of subjects in the 20 mg group, 3.4% (6 of 175) of subjects in the 30 mg group, and 2.3% (4 of 176) of subjects in the placebo group. The main events reported were headache (0.6% [1 of 175] in the 20 mg group, 1.7% [3 of 175] in the 30 mg group), nausea (1.1% [2 of 175] in the 20 mg group, 1.1% [2 of 175] in the 30 mg group), and diarrhoea (1.1% [2 of 175] in the 20 mg group, 1.1% [2 of 175] in the 30 mg group).

Adverse drug reactions were reported by 22.9% (40 of 175) of subjects in the 20 mg group, 33.1% (58 of 175) of subjects in the 30 mg group, and 14.2% (25 of 176) of subjects in the placebo group.

**Table 58. Adverse events reported by ≥3% of subjects in either of the apremilast groups within 24 weeks after the start of administration (safety analysis population)**

| | 20 mg (n = 175) | 30 mg (n = 175) | Placebo (n = 176)[a)] |
|---|---|---|---|
| Nausea | 16 (9.1) | 28 (16.0) | 4 (2.3) |
| Diarrhoea | 12 (6.9) | 21 (12.0) | 3 (1.7) |
| Dyspepsia | 8 (4.6) | 0 | 2 (1.1) |
| Headache | 6 (3.4) | 15 (8.6) | 4 (2.3) |
| Upper respiratory tract infection | 6 (3.4) | 7 (4.0) | 4 (2.3) |
| Cough | 6 (3.4) | 4 (2.3) | 2 (1.1) |
| Sinusitis | 6 (3.4) | 4 (2.3) | 1 (0.6) |

Number of subjects (%)

a) Includes events that occurred by Week 16 in subjects with early escape.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Acceptability of foreign clinical data

The applicant's explanation on the clinical data package in the present application:

Given that there are no major differences in the definition of psoriasis, diagnostic criteria, or therapeutic system between Japan and foreign countries (*The Japanese journal of dermatology*. 2011;121:1561-72, *J Am Acad Dermatol*. 2008;58:826-50), it was considered appropriate to develop apremilast in Japan by the bridging strategy based on the "Ethnic Factors in the Acceptability of Foreign Clinical Data" (PMSB/ELD Notification No. 672 dated August 11, 1998). With the foreign phase II study (Study CC-10004-PSOR-005) positioned as the study to be bridged, the Japanese phase II study (Study CC-10004-PSOR-011) was planned and conducted as the bridging study. If the bridging was established by the comparison of the results of both studies, the clinical data package in Japan was to be constructed by extrapolating the data of 2 foreign phase III studies (Studies CC-10004-PSOR-008 and CC-10004-PSOR-009) to the Japanese patients. Also, taking account of the limited number of patients with psoriatic arthritis in Japan, precluding the conduct of a confirmatory study on this patient group, patients with psoriatic arthritis were included in the Japanese phase II study (Study CC-10004-PSOR-011) to investigate the efficacy and safety. In addition, data of 4 foreign phase III studies (Studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005) in patients with psoriatic arthritis were included in the clinical data package.

The applicant's explanation on the extrapolation of the data of foreign clinical studies:

The prerequisites for the bridging to be established were (1) A statistically significant difference was observed in the PASI 75 response rate at Week 16, the primary endpoint, in the paired comparison between the placebo group and the apremilast group both in the bridging study (Study CC-10004-PSOR-011) and in the study to be bridged (Study CC-10004-PSOR-005) and (2) the safety profile was not significantly different between the bridging study and the study to be bridged. Table 59 shows PASI 75 response rates at Week 16 of administration in the bridging study and the study to be bridged. Thus, a statistically significant difference was observed in the rate in the paired comparison between the placebo group and each of the apremilast 20 and 30 mg groups in both studies. In the Japanese phase II study, the PASI 75 response rate tended to be lower compared with that observed in the foreign phase II studies. However, as shown in Table 23, there was no significant difference in the secondary endpoints in both studies, and there was no significant difference in the data between the Japanese phase II study and the foreign phase III study. Based on the above, the applicant considered that the observed data do not indicate the lower efficacy of apremilast in the Japanese.

As for safety, the main adverse events observed were gastrointestinal disorders such as diarrhoea in both studies, as shown in Tables 31 and 35 [see "7.2.2 Japanese phase II study" and "7.2.3 Foreign phase II study"], and the incidences of adverse events did not tend to differ significantly between the two studies. Also, there was no commonly reported adverse event in the Japanese phase II study.

**Table 59. PASI 75 response rate at Week 16 of administration in the bridging study (Japanese phase II study) and the study to be bridged (foreign phase II study) (efficacy analysis population, LOCF)**

| | 20 mg | 30 mg | Placebo |
|---|---|---|---|
| Japanese phase II study<br>(bridging study) | 23.5 (20/85) | 28.2 (24/85) | 7.1 (6/84) |
| Difference from placebo [95% CI]<br>*P* value | 16.4 [5.8, 27.0]<br>*P* = 0.0032 | 21.1 [10.1, 32.1]<br>*P* = 0.0003 | |
| Foreign phase II study<br>(study to be bridged) | 28.7 (25/87) | 40.9 (36/85) | 5.7 (5/88) |
| Difference from placebo [95% CI]<br>*P* value | 23.1 [12.4, 33.7]<br>*P* < 0.0001 | 35.2 [23.9, 46.6]<br>*P* < 0.0001 | |

% (number of subjects)

a) Chi-square test

b) Adjusted for multiplicity using Hochberg's method
Adjusted for multiplicity by a fixed rank test with the rank defined in the order of paired comparison between the placebo group and the 20 mg group, the 30 mg group, and the 10 mg group

Comparison of the subject characteristics between the 2 studies showed that the values of the following parameters tended to be lower in the bridging study than in the study to be bridged: Percentage of female subjects (20.5% in Japanese, 37.2% in non-Japanese), duration of psoriasis (13.0 ± 9.7 years, 19.0 ± 12.0 years), body weight (69.9 ± 13.2 kg, 91.8 ± 22.1 kg), BMI (25.1 ± 4.2, 31.2 ± 7.1), percentage of subjects with a history of psoriatic arthritis (3.5%, 21.0%), percentage of subjects with a history of systemic therapy (32.3%, 50.0%); and the values of the following parameters tended to be higher in the bridging study than in the study to be bridged: Age (50.8 ± 12.5 years, 44.3 ± 13.7 years), baseline PASI score (21.2 ± 9.2, 18.5 ± 6.6), and percentage of lesioned area relative to the body surface area (30.0 ± 16.4%, 22.0 ± 12.8%). Table 60 shows the results of the subpopulation analysis of each characteristic. The results suggested that none of the patient characteristics tested affected the efficacy and that the difference in the parameter values observed between the 2 studies did not affect the efficacy evaluation.

Based on the above, the applicant determined that the requirements for the establishment of the bridging were met and that it was appropriate to construct the clinical data package in Japan using the data of foreign phase III studies, etc.

**Table 60. Results of subpopulation analysis of PASI 75 response rate at Week 16 of administration in the bridging study (Japanese phase II study) and the study to be bridged (foreign phase II study) (efficacy analysis population, LOCF)**

| Subject characteristic | | Japanese phase II study | | | Foreign phase II study | | |
|---|---|---|---|---|---|---|---|
| | | Placebo | 20 mg | 30 mg | Placebo | 20 mg | 30 mg |
| Age | <65 years | 5.3 (4/75) | 16.9 (11/65) | 25.4 (18/71) | 6.2 (5/81) | 25.9 (21/81) | 38.0 (30/79) |
| | ≥65 years | 22.2 (2/9) | 45.0 (9/20) | 42.9 (6/14) | 0 (0/7) | 66.7 (4/6) | 66.7 (6/9) |
| Sex | Male | 9.7 (6/62) | 17.4 (12/69) | 23.9 (17/71) | 1.9 (1/53) | 21.8 (12/55) | 36.0 (18/50) |
| | Female | 0 (0/22) | 50.0 (8/16) | 50.0 (7/14) | 11.4 (4/35) | 40.6 (13/32) | 47.4 (18/38) |
| Duration of psoriasis | <10 years | 10.5 (4/38) | 23.9 (11/46) | 31.3 (10/32) | 25.0 (4/16) | 32.0 (8/25) | 33.3 (8/24) |
| | ≥10 years and <20 years | 3.6 (1/28) | 23.5 (4/17) | 37.5 (12/32) | 0 (0/32) | 33.3 (7/21) | 39.1 (9/23) |
| | ≥20 years | 5.6 (1/18) | 22.7 (5/22) | 9.5 (2/21) | 2.5 (1/40) | 25.0 (10/40) | 46.3 (19/41) |
| Body weight | <60 kg | 3.8 (1/26) | 33.3 (5/15) | 18.8 (3/16) | 0 (0/4) | 60.0 (3/5) | 42.9 (3/7) |
| | 60-85 kg | 10.2 (5/49) | 19.6 (11/56) | 31.7 (19/60) | 5.4 (2/37) | 32.4 (12/37) | 28.1 (9/32) |
| | >85 kg | 0 (0/9) | 28.6 (4/14) | 22.2 (2/9) | 6.4 (3/47) | 22.7 (10/44) | 49.0 (24/49) |
| BMI | <25 | 6.1 (3/49) | 24.4 (10/41) | 30.2 (13/43) | 11.1 (2/18) | 53.3 (8/15) | 30.0 (6/20) |
| | 25-35 | 9.4 (3/32) | 21.4 (9/42) | 26.2 (11/42) | 5.8 (3/52) | 26.3 (15/57) | 41.9 (18/43) |
| | >35 | 0 (0/3) | 50.0 (1/2) | 0 (0/0) | 0 (0/18) | 14.3 (2/14) | 48.0 (12/25) |
| History of psoriatic arthritis | Yes | 0 (0/2) | 0 (0/3) | 25.0 (1/4) | 0 (0/17) | 18.8 (3/16) | 38.1 (8/21) |
| | No | 7.3 (6/82) | 24.4 (20/82) | 28.4 (23/81) | 7.0 (5/71) | 31.0 (22/71) | 41.8 (28/67) |
| History of systemic therapy | Yes | 9.7 (6/62) | 25.5 (13/51) | 35.6 (21/59) | 2.6 (1/39) | 23.3 (10/43) | 34.0 (16/47) |
| | No | 0 (0/22) | 20.6 (7/34) | 11.5 (3/26) | 8.2 (4/49) | 34.1 (15/44) | 48.8 (20/41) |
| Baseline PASI score | ≤20 | 7.1 (4/56) | 20.5 (9/44) | 23.4 (11/47) | 4.5 (3/66) | 28.6 (20/70) | 43.9 (29/66) |
| | >20 | 7.1 (2/28) | 26.8 (11/41) | 34.2 (13/38) | 9.1 (2/22) | 29.4 (5/17) | 31.8 (7/22) |
| Percentage of lesioned area at baseline relative to the body surface area | ≤20% | 6.1 (2/33) | 19.4 (6/31) | 25.9 (7/27) | 5.3 (3/57) | 27.3 (15/55) | 46.8 (22/47) |
| | >20% | 7.8 (4/51) | 25.9 (14/54) | 29.3 (17/58) | 6.5 (2/31) | 32.3 (10/31) | 34.1 (14/41) |

% (number of subjects)

PMDA accepted the applicant's explanation of the bridging strategy and concluded that it is appropriate to construct the clinical data package by extrapolating the results of the foreign phase III study, etc., to Japanese patients with psoriasis and to evaluate the efficacy and safety of apremilast in Japanese patients with psoriasis based on the data package.

### 7.R.2 Efficacy

#### 7.R.2.1 Efficacy for plaque rash

The applicant's explanation on the efficacy of apremilast for plaque rash in patients with psoriasis vulgaris and in patients with psoriatic arthritis:

In the Japanese phase II study in patients with psoriasis vulgaris with plaque rash and patients with psoriatic arthritis with plaque rash (Study CC-10004-PSOR-011), a statistically significant difference was observed in the paired comparison of the PASI 75 response rate, the endpoint for evaluating the skin symptoms, between the placebo group and each of the apremilast 20 and 30 mg groups. Results of the foreign phase III studies (Studies CC-10004-PSOR-008 and CC-10004-PSOR-009) demonstrated the superiority of apremilast 30 mg to placebo in the PASI 75 response rate at Week 16 of administration, the primary endpoint. In both Japanese and foreign clinical studies, the apremilast 30 mg group was superior to the placebo group in PASI 50, PASI 90 and sPGA (0 or 1) response rates, the secondary

endpoints [see “7.2.2 Japanese phase II study,” “7.2.3 Foreign phase II study,” “7.3.1 Foreign phase III study,” and “7.3.2 Foreign phase III study”].

Table 61 shows the results with skin symptoms in patients with psoriatic arthritis with plaque rash (1 subject in the placebo group, 2 subjects in the 20 mg group, and 2 subjects in the 30 mg group) enrolled in the Japanese phase II study (Study CC-10004-PSOR-011). All patients, albeit in a limited number, showed a tendency of improvement. In the foreign phase III study (Study CC-10004-PSA-004) which enrolled patients with psoriatic arthritis with one or more plaque rashes of ≥2 cm in size, skin symptoms were evaluated in patients with the rash covering ≥3% of the body surface area. In this study, the PASI 75 response rate at Week 16 of administration was 20.9% (19 of 91) of subjects in the apremilast 20 mg group, 22.2% (20 of 90) of subjects in the 30 mg group, and 7.9% (7 of 89) of subjects in the placebo group, demonstrating a tendency of improvement in the apremilast groups compared with the placebo group.

Based on the above, the applicant considers that the efficacy of apremilast for plaque rash in patients with psoriasis vulgaris and in patients with psoriatic arthritis has been established.

**Table 61. Results with skin symptoms in patients with psoriatic arthritis enrolled in Study CC-10004-PSOR-011**

| Case No. | Dose | Comparison of skin symptoms with those at baseline |
|---|---|---|
| 1481003[a)] | Placebo/20 mg | PASI score improved by 29% at Week 16 (placebo administration period), PASI 50 achieved at Week 24 (Week 8 of apremilast administration), and PASI 90 achieved at Week 52. |
| 1011012 | 20 mg | PASI score improved by 44% at Week 16 and PASI 50 achieved at Week 52. |
| 1211004 | 20 mg | PASI score worsened by 52% at Week 16 but improved by 33% at Week 52. |
| 1231004[b)] | 30 mg | PASI score improved by 22% at Week 16. |
| 1201004 | 30 mg | PASI 50 achieved at Week 16. |

a) Placebo was administered up to Week 16.
b) Study discontinued at Week 24.

PMDA accepted the explanation of the applicant and concluded that the efficacy of apremilast for plaque rash in patients with psoriasis vulgaris and in patients with psoriatic arthritis has been demonstrated.

### 7.R.2.2 Efficacy for joint symptoms of psoriatic arthritis

The applicant’s explanation on the efficacy of apremilast in patients with psoriatic arthritis:
Table 62 shows the results with joint symptoms in patients with psoriatic arthritis (1 subject in the placebo group, 2 subjects in the 20 mg group, and 2 subjects in the 30 mg group) enrolled in the Japanese phase II study (Study CC-10004-PSOR-011). Although only a limited number of subjects were investigated, all of them except case number 1231004 generally showed a tendency of improvement following apremilast administration. Neither of the 2 subjects available for ACR evaluation (1 in the 20 mg group, 1 in the 30 mg group) achieved ACR 20 at Week 16, but the subject in the 30 mg group achieved ACR 20 at Week 24.

**Table 62. Results with joint symptoms in patients with psoriatic arthritis enrolled in Study CC-10004-PSOR-011**

| Case No. | Dose | Comparison of joint symptoms with those at baseline |
|---|---|---|
| 1481003[a)] | Placebo/20 mg | Pain VAS score worsened by 21% at Week 16 (placebo administration period), but improved by 50% at Week 24 (Week 8 of apremilast administration) and by 62% at Week 52. Tender joint count improved by 100% from Week 40 on. |
| 1011012 | 20 mg | Pain VAS score improved by 10% at Week 16.<br>No improvement observed in swollen joints, but painful joint count improved by 100% at Week 52. |
| 1211004[b)] | 20 mg | Pain VAS score improved by only 3.8% at Week 16, but by 81% at Week 52. |
| 1231004[c)] | 30 mg | Neither tender joint count nor pain VAS score improved at Week 16. |
| 1201004 | 30 mg | Tender joint count improved by 75% and swollen joint count by 100% at Week 16. Pain VAS did not improve, but ACR 20 achieved at Week 24. |

VAS: visual analog scale
a) Placebo was administered up to Week 16. No swollen joint was observed at baseline.
b) Neither swollen joints nor tender joints were evaluated at baseline.
c) The study was discontinued at Week 24. No swollen joint was observed at baseline.

Results of the foreign phase III studies conducted in patients with psoriatic arthritis (Studies CC-10004-PSA-002, CC-10004-PSA-003, and CC-10004-PSA-004) demonstrated the superiority of apremilast to

placebo in the ACR 20 response rate at Week 16, the primary endpoint [see "7.3.4 Foreign phase III study," "7.3.5 Foreign phase III study," and "7.3.6 Foreign phase III study"]. Taking account of these findings, apremilast is expected to be effective in Japanese patients with psoriatic arthritis.

PMDA's view:
Given the small number of patients with psoriatic arthritis in Japan, it is understandably difficult to conduct an independent bridging study on Japanese patients with psoriatic arthritis. Therefore, it is inevitable to estimate the efficacy of apremilast in Japanese patients with psoriatic arthritis based on the results obtained from patients with psoriatic arthritis enrolled in the Japanese phase II study (Study CC-10004-PSOR-011) and on the results of the foreign phase III studies in patients with psoriatic arthritis (Studies CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005). Although only an extremely limited number of Japanese patients with psoriatic arthritis were enrolled in the Japanese phase II study, results showed a tendency of improvement in joint symptoms. Also, all of the 3 foreign phase III studies demonstrated the superiority of apremilast to placebo. Taking account of these findings, PMDA concludes that apremilast has a certain level of efficacy for joint symptoms in Japanese patients with psoriatic arthritis. However, because of the limited data available on Japanese patients with psoriatic arthritis, efficacy of apremilast for joint symptoms in patients with psoriatic arthritis should be investigated in the post-marketing surveillance, etc.

### 7.R.3 Safety

The applicant's explanation on the safety of apremilast, based on the following data: (i) Pooped data of all phase II and III studies in patients with psoriasis vulgaris or psoriatic arthritis except Studies CC-10004-PSOR-010 and CC-10004-PSOR-011 (Studies CC-10004-PSOR-001,[31)] CC-10004-PSOR-003, CC-10004-PSOR-004, CC-10004-PSOR-005, CC-10004-PSOR-008, CC-10004-PSOR-009, CC-10004-PSA-001, CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005) and a phase II study in patients with rheumatoid arthritis (Study CC-10004-RA-002) (apremilast pooled analysis), (ii) pooled data of foreign phase III studies in patients with psoriasis with plaque rash (Studies CC-10004-PSOR-008 and CC-10004-PSOR-009) (PSOR Phase 3 pooled analysis), (iii) pooled data of foreign phase III studies in patients with psoriatic arthritis (Studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005) (PsA Phase 3 pooled analysis), and (iv) the Japanese phase II study in patients with psoriasis with plaque rash (Japanese study PSOR-011):
Table 63 shows the incidences of adverse events during the placebo-controlled period[32)] and apremilast administration period[33)] in the apremilast pooled analysis, and Table 64 shows the incidences of adverse events in the Japanese study PSOR-011. No particular difference was observed in the incidences of adverse events between the apremilast pooled analysis and the Japanese study PSOR-011.

**Table 63. Incidences of adverse events in apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort[a)] |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Death | 1 (0.1) | 1 (0.1) | 2 (0.1) | 3 (0.2) | 6 (0.3) | 9 (0.2) |
| Adverse events | 628 (62.9)<br>298.7 | 1,098 (65.8)<br>388.0 | 761 (53.9)<br>275.8 | 1124 (77.5)<br>144.2 | 1966 (83.4)<br>174.0 | 3311 (81.0)<br>170.2 |
| Serious adverse events | 35 (3.5)<br>9.4 | 45 (2.7)<br>7.9 | 49 (3.5)<br>11.5 | 176 (12.1)<br>7.8 | 276 (11.7)<br>6.7 | 459 (11.2)<br>7.1 |
| Adverse events leading to discontinuation | 60 (6.0)<br>16.0 | 107 (6.4)<br>18.8 | 64 (4.5)<br>15.0 | 142 (9.8)<br>5.9 | 268 (11.4)<br>6.1 | 431 (10.5)<br>6.3 |
| Adverse drug reaction | 295 (29.5)<br>99.1 | 638 (38.2)<br>160.3 | 280 (19.8)<br>75.2 | 510 (35.2)<br>29.4 | 1046 (44.4)<br>37.8 | 1650 (40.4)<br>36.0 |
| Total exposure period (subject-years) | 377.4 | 574.5 | 429.5 | 2,416.0 | 4391.7 | 6927.4 |

Upper row, number of subjects (%); lower row, incidence per 100 subject-years adjusted for total exposure period
a) Sum of subjects receiving apremilast at any dose in the entire evaluation period.

31) The study investigating the pharmacodynamics and safety in apremilast 20 mg once daily oral administration for 29 days to patients with psoriasis with plaque rash
32) Data collected during the placebo-controlled period from subjects who received ≥1 dose of the allocated study drug. Data of subjects in the placebo group with early escape were collected up to the time of the early escape.
33) Data collected from the start of apremilast up to cut-off from all subjects who received ≥1 dose of apremilast.

**Table 64. Incidences of adverse events in the Japanese study PSOR-011 (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | |
|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort |
| Number of subjects | 85 | 85 | 84 | 121 | 120 |
| Death | 0 | 0 | 0 | 1 (0.8) | 0 |
| Adverse events | 49 (57.6)<br>340.1 | 44 (51.8)<br>290.2 | 35 (41.7)<br>201.2 | 94 (77.7)<br>182.4 | 89 (74.2)<br>154.2 |
| Serious adverse events | 4 (4.7)<br>18.1 | 0 | 0 | 11 (9.1)<br>9.6 | 2 (1.7)<br>1.6 |
| Adverse events leading to discontinuation | 10 (11.8)<br>44.8 | 6 (7.1)<br>25.1 | 4 (4.8)<br>17.3 | 19 (15.7)<br>16.1 | 10 (8.3)<br>7.9 |
| Adverse drug reactions | 18 (21.2)<br>93.6 | 25 (29.4)<br>135.5 | 8 (9.5)<br>37.2 | 34 (28.1)<br>34.9 | 37 (30.8)<br>39.4 |
| Total exposure period (subject-years) | 22.5 | 24.0 | 23.3 | 118.0 | 126.5 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period

Tables 65 and 66 show main adverse events observed in the apremilast pooled analysis. During the placebo-controlled period, the incidences of nausea, vomiting, diarrhoea, headache, and upper respiratory tract infection tended to be higher in the apremilast group than in the placebo group. During the apremilast administration period, the incidences of diarrhoea, nausea, and upper respiratory tract infection tended to be higher in the apremilast 30 mg cohort than in the 20 mg cohort.

**Table 65. Adverse events reported by ≥3% of subjects in either of the apremilast groups during the placebo-controlled period in the apremilast pooled analysis (safety analysis population)**

| | 20 mg<br>(n = 999) | 30 mg<br>(n = 1668) | Placebo<br>(n = 1411) |
|---|---|---|---|
| Diarrhoea | 108 (10.8) | 252 (15.1) | 60 (4.3) |
| Nausea | 103 (10.3) | 273 (16.4) | 81 (5.7) |
| Headache | 89 (8.9) | 133 (8.0) | 67 (4.7) |
| Upper respiratory tract infection | 59 (5.9) | 126 (7.6) | 55 (3.9) |
| Nasopharyngitis | 58 (5.8) | 93 (5.6) | 84 (6.0) |
| Dyspepsia | 30 (3.0) | 43 (2.6) | 19 (1.3) |
| Vomiting | 27 (2.7) | 62 (3.7) | 18 (1.3) |
| Tension headache | 4 (0.4) | 77 (4.6) | 21 (1.5) |

Number of subjects (%)

**Table 66. Adverse events with an incidence of ≥3 per 100 subject-years adjusted for the total exposure period during the apremilast administration period in the apremilast pooled analysis (safety analysis population)**

| | 20 mg cohort<br>(n = 1450) | 30 mg cohort<br>(n = 2357) | Apremilast cohort<br>(n = 4089) |
|---|---|---|---|
| Diarrhoea | 183 (12.6)<br>8.5 | 389 (16.5)<br>10.3 | 614 (15.0)<br>10.2 |
| Upper respiratory tract infection | 168 (11.6)<br>7.8 | 381 (16.2)<br>10.0 | 569 (13.9)<br>9.4 |
| Nausea | 166 (11.4)<br>7.5 | 394 (16.7)<br>10.4 | 601 (14.7)<br>9.8 |
| Nasopharyngitis | 163 (11.2)<br>7.4 | 315 (13.4)<br>8.1 | 525 (12.8)<br>8.4 |
| Headache | 157 (10.8)<br>7.1 | 226 (9.6)<br>5.6 | 428 (10.5)<br>6.7 |
| Hypertension | 85 (5.9)<br>3.7 | 144 (6.1)<br>3.5 | 237 (5.8)<br>3.6 |
| Bronchitis | 75 (5.2)<br>3.2 | 138 (5.9)<br>3.3 | 217 (5.3)<br>3.3 |
| Sinusitis | 72 (5.0)<br>3.1 | 124 (5.3)<br>3.0 | 203 (5.0)<br>3.1 |
| Back pain | 62 (4.3)<br>2.7 | 132 (5.6)<br>3.1 | 203 (5.0)<br>3.1 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period

Death occurred in 11 subjects receiving apremilast in foreign clinical studies (cerebrovascular accident [2 subjects], haemorrhage intracranial,[34)] cardiogenic shock/myocardial infarction/respiratory failure/sepsis, cardiac failure, cardiac arrest/cardiac failure congestive/mitral valve stenosis, multi-organ failure, myocardial infarction/arrhythmia/hypertensive cardiomyopathy, chest injury/neck trauma/road traffic accident, cerebral infarction, and acute myeloid leukaemia[35)] [1 subject each]). A causal relationship to the study drug was ruled out for all of these events in 10 subjects except cardiac failure. In the Japanese study PSOR-011, 1 subject died of metastatic lung cancer, and a causal relationship of the death to the study drug could not be ruled out.

Serious adverse events were observed in 11.2% (459 of 4089) of subjects during the apremilast administration period in the apremilast pooled analysis. Main serious adverse events included osteoarthritis in 0.4% of subjects (17 subjects, 0.2 per 100 subject-years), psoriatic arthropathy in 0.3% of subjects (13 subjects, 0.2 per 100 subject-years), psoriasis in 0.3% of subjects (12 subjects, 0.2 per 100 subject-years), cholelithiasis in 0.3% of subjects (11 subjects, 0.2 per 100 subject-years), and coronary artery disease in 0.3% of subjects (11 subjects, 0.2 per 100 subject-years). In the Japanese study PSOR-011, serious adverse events were observed in 5.4% (13 of 241) of subjects (cholelithiasis, cholelithiasis/bile duct stone, metastatic lung cancer, colon cancer/metastatic colon cancer/pneumothorax, intraocular pressure increased, intervertebral disc protrusion, periodontitis, arthritis bacterial, cerebral haemorrhage, coronary artery stenosis, renal infarct, cardiac failure congestive/pneumonia, and diabetes mellitus).

Taking account of the pharmacological action of apremilast and of the incidences of adverse events in clinical studies, PMDA reviewed the following events.

### 7.R.3.1 Infection

The applicant's explanation on the incidences of infection following the administration of apremilast:
Tables 67 and 68 show the incidences of main adverse events classified as "Infections and infestations (system organ class [SOC])" in the apremilast pooled analysis and in the Japanese study PSOR-011. Most of the events were mild or moderate in severity.

**Table 67. Incidences of infections and infestations (SOC), etc., in apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Infections and infestations (SOC) | 253 (25.3)<br>77.3 | 455 (27.3)<br>93.3 | 318 (22.5)<br>84.2 | 644 (44.4)<br>44.5 | 1226 (52.0)<br>49.8 | 1979 (48.4)<br>49.6 |
| Upper respiratory tract infection | 59 (5.9)<br>16.2 | 126 (7.6)<br>22.8 | 55 (3.9)<br>13.1 | 168 (11.6)<br>7.8 | 381 (16.2)<br>10.0 | 569 (13.9)<br>9.4 |
| Nasopharyngitis | 58 (5.8)<br>15.8 | 93 (5.6)<br>16.7 | 84 (6.0)<br>20.1 | 163 (11.2)<br>7.4 | 315 (13.4)<br>8.1 | 525 (12.8)<br>8.4 |
| Bronchitis | 21 (2.1)<br>5.6 | 23 (1.4)<br>4.0 | 11 (0.8)<br>2.6 | 75 (5.2)<br>3.2 | 138 (5.9)<br>3.3 | 217 (5.3)<br>3.3 |
| Sinusitis | 20 (2.0)<br>5.3 | 36 (2.2)<br>6.3 | 22 (1.6)<br>5.2 | 72 (5.0)<br>3.1 | 124 (5.3)<br>3.0 | 203 (5.0)<br>3.1 |
| Serious infection | 3 (0.3)<br>0.8 | 6 (0.4)<br>1.0 | 5 (0.4)<br>1.2 | 25 (1.7)<br>1.0 | 41 (1.7)<br>0.9 | 67 (1.6)<br>1.0 |
| Upper respiratory tract infection (SCQ) | 158 (15.8)<br>45.8 | 295 (17.7)<br>56.5 | 182 (12.9)<br>45.4 | 419 (28.9)<br>23.5 | 824 (35.0)<br>26.8 | 1321 (32.3)<br>26.7 |
| Opportunistic infection (SCQ) | 11 (1.1)<br>2.9 | 9 (0.5)<br>1.6 | 16 (1.1)<br>3.7 | 44 (3.0)<br>1.9 | 72 (3.1)<br>1.7 | 125 (3.1)<br>1.8 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period; -, Not calculated or <0.05

34) Haemorrhage intracranial occurred during placebo administration after apremilast administration.
35) Acute myeloid leukaemia occurred in an investigator-initiated clinical study in patients with rheumatoid arthritis.

**Table 68. Incidences of infections and infestations (SOC), etc., in Japanese study PSOR-011 (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | |
|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort |
| Number of subjects | 85 | 85 | 84 | 121 | 120 |
| Infections and infestations (SOC) | 16 (18.8)<br>81.6 | 18 (21.2)<br>87.4 | 13 (15.5)<br>61.9 | 47 (38.8)<br>54.8 | 51 (42.5)<br>57.3 |
| Upper respiratory tract infection | 0<br>- | 0<br>- | 0<br>- | 0<br>- | 0<br>- |
| Nasopharyngitis | 10 (11.8)<br>49.0 | 10 (11.8)<br>45.4 | 7 (8.3)<br>31.5 | 28 (23.1)<br>28.7 | 35 (29.2)<br>34.7 |
| Bronchitis | 0<br>- | 0<br>- | 1 (1.2)<br>4.3 | 3 (2.5)<br>2.6 | 1 (0.8)<br>0.8 |
| Sinusitis | 0<br>- | 1 (1.2)<br>4.2 | 0<br>- | 2 (1.7)<br>1.7 | 2 (1.7)<br>1.6 |
| Serious infection | 1 (1.2)<br>4.5 | 0<br>- | 0<br>- | 2 (1.7)<br>1.7 | 1 (0.8)<br>0.8 |
| Upper respiratory tract infection (SCQ) | 11 ( 12.9)<br>54.3 | 11 ( 12.9)<br>50.5 | 7 ( 8.3)<br>31.5 | 32 (26.4)<br>34.1 | 38 (31.7)<br>38.6 |
| Opportunistic infection (SCQ) | 0<br>- | 1 ( 1.2)<br>4.2 | 0<br>- | 2 (1.7)<br>1.7 | 3 (2.5)<br>2.4 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period; -, Not calculated or <0.05

Regarding serious infections, the incidence of serious adverse events classified as "Infections and infestations (SOC)" during the apremilast administration period in the apremilast pooled analysis was 1.7% of subjects in the 20 mg cohort (25 of 1450, 1.0 per 100 subject-years) and 1.7% of subjects in the 30 mg cohort (41 of 2357, 0.9 per 100 subject-years). Main events included pneumonia in 10 subjects (4 in the 20 mg cohort, 6 in the 30 mg cohort), appendicitis in 6 subjects (2 in the 20 mg cohort, 4 in the 30 mg cohort), diverticulitis in 5 subjects (3 in the 20 mg cohort, 2 in the 30 mg cohort). The incidence of serious adverse events classified as "Infections and infestations (SOC)" during the apremilast administration period in the Japanese study PSOR-011 was 1.7% (2 of 121) of subjects in the 20 mg group (arthritis bacterial and pneumonia). In the foreign post-marketing safety data, serious infection was observed in 0.2% (240 of 104,754) of patients receiving apremilast. The main events observed were pneumonia (33 patients), upper respiratory tract infection (26 patients), and bronchitis (23 patients), with the incidence of infection showing no tendency of increase after the market launch in foreign countries.

As for tuberculosis,[36] the Japanese study PSOR-011 included 1 subject with a history of tuberculosis, but this subject did not show any adverse events classified as infections (high level terms [HLT])." In the apremilast pooled analysis, 31 subjects (0.7%) had a history of tuberculosis (e.g., latent tuberculosis, pulmonary tuberculosis, disseminated tuberculosis) and 16 subjects (0.4%) were positive for tuberculin skin test, but none of the subjects showed reactivation of tuberculosis during the entire observation period. Among subjects without a history of tuberculosis, 4 subjects were QuantiFERON positive, and 1 subject was tuberculin skin test positive, during the study period. All of them were treated with antituberculosis drugs, and none of them had adverse events classified as "Tuberculous infections (HLT)." In the foreign post-marketing safety data (104,754 patients), there were tuberculosis (3 patients), latent tuberculosis (1 patient), and serious tuberculosis (2 patients). One patient with a history of tuberculosis had a relapse of tuberculosis, but details including administration of apremilast were unclear. Based on the above, the applicant considers that, currently, apremilast is unlikely to induce tuberculosis in *Mycobacterium tuberculosis*-naïve individuals or in patients with latent tuberculosis.

As for viral liver diseases,[37] the foreign post-marketing safety data (104,754 patients) included 11 and 50 patients with past/current hepatitis B or C, respectively, who were treated with apremilast. None of them showed relapse of the disease. Based on the above, the applicant considers that, currently, apremilast is unlikely to induce hepatitis reactivation in patients with a past history of hepatitis B or C.

In foreign countries including the US and Europe, screening tests for tuberculosis and hepatitis B and C are not required before apremilast administration. No safety concerns are raised from the foreign post-marketing safety data which are considered to have been collected from patients treated with apremilast without the screening tests in advance. Taking account of these situations, the applicant considers that

[36] Subjects with active or insufficiently treated tuberculosis were excluded from the clinical studies of apremilast.
[37] Subjects positive for hepatitis B surface antigen or for anti-hepatitis C virus antibody were excluded from the clinical studies.

screening tests for tuberculosis or hepatitis B and C are not required before apremilast administration in Japan.

PMDA's view:
In light of the facts that (1) apremilast has a pharmacological effect to suppress multiple inflammatory cytokines to a certain extent, that (2) the incidence of infection tends to be higher in the apremilast group than in the placebo group, and that (3) serious infection occurred among subjects receiving apremilast, caution should be exercised against the occurrence of infection during apremilast administration, and patients should be closely followed up when apremilast is administered to patients with infection, patients suspected to have infection, and patients with a history of recurrent infection. Nevertheless, given the foreign post-marketing safety data and other available information, PMDA considers that, currently, there is little evidence to recommend mandatory screening tests for tuberculosis, hepatitis B, or hepatitis C before administration in all patients undergoing treatment with apremilast. Because (1) only a limited number of subjects have been investigated, (2) the possibility of apremilast inducing infection cannot be excluded judging from its mechanism of action, and (3) serious infections have been reported, occurrences of infections should be continuously investigated in the post-marketing surveillance.

### 7.R.3.2 Gastrointestinal disorders

The applicant's explanation on the incidences of gastrointestinal disorders following apremilast administration:
Diarrhoea is considered to be induced by apremilast according to the following mechanism: Apremilast increases intracellular cAMP, which activates $Cl^-$ channel on the small intestinal crypts and, with $Cl^-$ transport, water is secreted into the intestinal tract, causing diarrhoea (*Am J Respir Cell Mol Biol.* 2014;50:549-58). Nausea and vomiting are supposed to be induced by the enhanced activity of neurons in the chemoreceptor trigger zone mediated by the increase in the intracellular cAMP due to PDE4 inhibition (*Bio Drugs.* 2013;27:359-73, *J Chem Neuroanat.* 2010;40:36-42) and by the action mediated by peripheral sympathetic nerves (*Br J Pharmacol*. 2002;135:113-8), but the detailed mechanism is unknown. Gastrointestinal disorders including diarrhoea, nausea, and abdominal pain are also reported as adverse events with roflumilast, another PDE4 inhibitor (*Lancet.* 2009,29;374:695-703).

In the foreign phase I study in healthy adult subjects (Study CC-10004-PK-007), the incidence of nausea during the 14-day once daily administration of apremilast 40 mg was 78% in the 40 mg QD group not undergoing gradual dose increase, whereas the incidence was 44% in the gradual dose increase group (10 mg once daily from Day 1 to Day 3, 20 mg once daily from Day 4 to Day 6, 40 mg once daily from Day 7 on), showing a tendency of a lower incidence of gastrointestinal disorder-related events in patients receiving apremilast by gradual dose increase. Therefore, in subsequent clinical studies, the treatment with apremilast was to be started by gradual dose increase [see "7.1 Phase I study"].

Tables 69 and 70 show the incidences of gastrointestinal disorder-related events in the apremilast pooled analysis and in the Japanese study PSOR-011. The incidence tended to be higher in the apremilast group than in the placebo group, and showed a dose-dependent increase. The incidence of gastrointestinal disorders (SOC) within 16 weeks of treatment was 37.9% (315 of 832) of subjects in the apremilast 30 mg group and 17.9% (75 of 418) of subjects in the placebo group in PSOR Phase 3 pooled analysis, and 22.6% (153 of 676) of subjects in the apremilast 20 mg group, 32.7% (220 of 672) of subjects in the 30 mg group, and 10.6% (71 of 671) of subjects in the placebo group in PsA Phase 3 pooled analysis. The incidence tended to be higher in the apremilast group both among patients with psoriasis vulgaris and among patients with psoriatic arthritis.

**Table 69. Incidences of gastrointestinal disorder-related events in apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Gastrointestinal disorders (SOC) | 250 (25.0)<br>82.2 | 607 (36.4)<br>149.6 | 210 (14.9)<br>54.4 | 469 (32.3)<br>26.5 | 1020 (43.3)<br>36.3 | 1583 (38.7)<br>34.0 |
| Diarrhoea (SCQ) | 110 (11.0)<br>31.9 | 276 (16.5)<br>55.7 | 60 (4.3)<br>14.4 | 188 (13.0)<br>8.7 | 422 (17.9)<br>11.4 | 652 (15.9)<br>10.9 |
| Gastrointestinal pain and abdominal pain (SCQ) | 43 (4.3)<br>11.7 | 84 (5.0)<br>15.2 | 31 (2.2)<br>7.3 | 85 (5.9)<br>3.7 | 167 (7.1)<br>4.0 | 265 (6.5)<br>4.0 |
| Nausea (PT) | 103 (10.3)<br>29.6 | 273 (16.4)<br>54.7 | 81 (5.7)<br>19.6 | 166 (11.4)<br>7.5 | 394 (16.7)<br>10.4 | 601 (14.7)<br>9.8 |
| Vomiting (PT) | 27 (2.7)<br>7.3 | 62 (3.7)<br>11.0 | 18 (1.3)<br>4.2 | 54 (3.7)<br>2.3 | 115 (4.9)<br>2.7 | 178 (4.4)<br>2.6 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period; -, Not calculated or <0.05

**Table 70. Incidences of gastrointestinal disorder-related events in Japanese study PSOR-011 (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | |
|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort |
| Number of subjects | 85 | 85 | 84 | 121 | 120 |
| Gastrointestinal disorders (SOC) | 14 (16.5)<br>69.3 | 17 (20.0)<br>84.3 | 8 (9.5)<br>36.0 | 29 (24.0)<br>29.7 | 30 (25.0)<br>29.3 |
| Diarrhoea (SCQ) | 5 (5.9)<br>23.5 | 5 (5.9)<br>21.7 | 0<br>- | 8 (6.6)<br>7.2 | 8 (6.7)<br>6.6 |
| Gastrointestinal pain and abdominal pain (SCQ) | 2 (2.4)<br>9.0 | 1 (1.2)<br>4.2 | 2 (2.4)<br>8.7 | 3 (2.5)<br>2.6 | 2 (1.7)<br>1.6 |
| Nausea (PT) | 1 (1.2)<br>4.5 | 2 (2.4)<br>8.5 | 3 (3.6)<br>13.1 | 3 (2.5)<br>2.6 | 3 (2.5)<br>2.4 |
| Vomiting (PT) | 0<br>- | 0<br>- | 1 (1.2)<br>4.3 | 0<br>- | 0<br>- |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period; -, Not calculated or <0.05

Gastrointestinal disorder-related serious adverse events were diarrhoea (3 subjects) and nausea (1 subject) during the apremilast administration period in the apremilast pooled analysis, and the outcome was recovery in 3 subjects with diarrhoea and unknown in 1 subject with nausea. No gastrointestinal disorder-related serious adverse event was observed in the Japanese study PSOR-011. Adverse events leading to discontinuation of the study drug were nausea in 1.6% (64 subjects) of subjects, diarrhoea in 1.2% (51 subjects) of subjects, and vomiting in 0.5% (19 subjects) of subjects during the apremilast administration period (4089 subjects) of the apremilast pooled analysis and diarrhoea in 1.2% (3 subjects) of subjects and nausea in 0.4% (1 subject) of subjects in the Japanese study PSOR-011 (241 subjects).

Among diarrhoea and nausea observed in the apremilast cohort, 61.5% (152 of 247) of subjects and 65.3% (147 of 225) of subjects, respectively, in PSOR Phase 3 pooled analysis and 56.5% (134 of 237) of subjects and 57.5% (134 of 233) of subjects, respectively, in PsA Phase 3 pooled analysis experienced and resolved within 4 weeks after the start of treatment.

Thus, gastrointestinal disorders such as diarrhoea and nausea are related to apremilast administration and show dose dependency. However, most of them were mild or moderate in severity, with serious events observed only in limited cases. Also, although the events were often observed during the early stage of apremilast administration, the treatment could be continued in most of the cases, and the events resolved during the continued administration, suggesting that they were of no particular clinical problems. Nevertheless, since starting the treatment with gradual dose increase is very effective in reducing the frequency of gastrointestinal disorders such as diarrhoea, the applicant plans to prepare sets of product sheets, each containing tablets for the first 14 days in accordance with the gradual dose increase up to Day 6, in order to facilitate the compliance of patients to the dosing schedule of apremilast.

PMDA's view:
The incidence of gastrointestinal disorder-related events tended to be higher in subjects receiving

apremilast than in subjects receiving placebo, and showed a dose-dependent increase. In addition, diarrhoea, nausea, and vomiting are observed also with roflumilast, a drug in the same class with PDE4-inhibiting activity. Therefore, careful attention should be paid to the occurrence of these events in administering apremilast. Furthermore, taking account of the observations that gastrointestinal disorder-related events occurred frequently within 4 weeks after the start of the treatment, requiring particular caution during the early stage of administration, and that the incidence tended to be higher when apremilast was not administered by the gradual dose increase during the early stage of the treatment [see "7.1 Phase I study"], appropriate cautions should be provided so that patients comply with the dosage regimen of the gradual dose increase during the early stage of the treatment with apremilast.

### 7.R.3.3 Headache

The applicant's explanation on the incidences of headache and tension headache following apremilast administration:

Headache is considered to be induced by the vasodilation due to the increase in intracellular cAMP caused by the inhibition of PDE4 in vascular smooth muscles, but the detailed mechanism is unknown (*J Headache Pain.* 2014;15:22). Headache is observed also with roflumilast, a drug in the same class (*Lancet.* 2009, 29;374:695-703, *Expert Opin Drug Saf.* 2016;15:1133-46). Since headache is related to the tolerability of drugs, occurrences of the event were investigated.

Table 71 shows the incidences of headache-related main adverse events in the apremilast pooled analysis. During the placebo-controlled period, the apremilast group showed a dose-dependently higher incidence compared with the placebo group. During the apremilast administration period, headache-related serious adverse events were headache (2 subjects), and tension headache and migraine (1 subject each). The outcome was recovery for headache, tension headache, and migraine (1 subject each) and unknown for headache (1 subject). During the placebo-controlled period in PSOR Phase 3 pooled analysis, the incidence of headache was 11.9% (141 of 1184) of subjects in the apremilast group and 6.7% (28 of 418) of subjects in the placebo group. During the placebo-controlled period in PsA Phase 3 pooled analysis, the incidence was 7.1% (138 of 1945) of subjects in the apremilast group and 3.6% (24 of 671) of subjects in the placebo group. The incidence tended to be higher in the apremilast group both among patients with psoriasis vulgaris and among patients with psoriatic arthritis.

**Table 71. Incidences of headache-related events in apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Headache | 89 (8.9)<br>25.3 | 133 (8.0)<br>24.7 | 67 (4.7)<br>16.2 | 157 (10.8)<br>7.1 | 226 (9.6)<br>5.6 | 428 (10.5)<br>6.7 |
| Tension headache | 4 (0.4)<br>1.1 | 77 (4.6)<br>13.8 | 21 (1.5)<br>4.9 | 8 (0.6)<br>0.3 | 138 (5.9)<br>3.3 | 150 (3.7)<br>2.2 |
| Migraine | 10 (1.0)<br>2.7 | 30 (1.8)<br>5.3 | 6 (0.4)<br>1.4 | 20 (1.4)<br>0.8 | 72 (3.1)<br>1.7 | 99 (2.4)<br>1.5 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period

In the Japanese study PSOR-011, the incidence of headache-related adverse events was 2.5% (3 of 121) of subjects in the 20 mg group, 1.7% (2 of 120) of subjects in the 30 mg group, and 2.4% (2 of 84) of subjects in the placebo group during the placebo-controlled period, and 3.3% (4 of 121) of subjects in the 20 mg cohort and 4.2% (5 of 120) of subjects in the 30 mg cohort during the apremilast administration period. No headache-related serious adverse events were observed in the Japanese study PSOR-011.

Among headache/tension headache, 72.6% (135 of 186 subjects) observed in PSOR Phase 3 pooled analysis and 71.4% (5 of 7) observed in the Japanese study PSOR-011 occurred and disappeared within 30 days after the start of treatment.

The above results indicate that although headache is related to apremilast administration, it is mild or moderate in most cases, and that although headache occurs frequently during the early stage of apremilast administration, it is possible to continue administration in most cases and headache resolved while the administration is continued. Based on the above, the applicant considers that headache does not pose any particular problem.

PMDA's view:
The incidence of headache tends to be higher in the apremilast group than in the placebo group, showing a dose-dependent increase. Careful attention should be paid to the occurrence of headache in administering apremilast. Since most of the events occurred within 30 days after the start of administration, particular attention should be paid during the early stage of the treatment. Given the limited number of subjects investigated currently, occurrences of headache should be continuously investigated in the post-marketing surveillance, etc.

### 7.R.3.4 Malignant tumor

The applicant's explanation on the risk of apremilast-associated malignant tumor:
In clinical studies in patients with psoriasis, the standardized incidence ratio of malignant tumor is reported to be 1.13 to 1.78 (*J Invest Dermatol.* 2001;117:1531-7, *Br J Cancer.* 2009;100:1499-502, *J Am Acad Dermatol.* 2012;66:AB6, *Br J Dermatol.* 1999;140:237-42, *Arch Dermatol.* 2001;137:778-83, *J Invest Dermatol.* 2009;129:2604-12), indicating a tendency of a higher risk of malignant tumor in patients with psoriasis vulgaris and patients with psoriatic arthritis. Taking account of these findings and the effect of apremilast on immune functions, the applicant investigated the occurrences of malignant tumor in subjects treated with apremilast.

Table 72 shows the incidences of malignant tumor-related events during the placebo-controlled period and the apremilast administration period in the apremilast pooled analysis. The incidence was similar between the placebo group and the apremilast group during the placebo-controlled period.

**Table 72. Malignant tumor-related events reported by ≥2 subjects receiving apremilast in the apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Malignant tumor (SCQ) | 3 (0.3)<br>0.8 | 8 (0.5)<br>1.4 | 5 (0.4)<br>1.2 | 25 (1.7)<br>1.0 | 44 (1.9)<br>1.0 | 71 (1.7)<br>1.0 |
| Prostatic specific antigen increased | 0<br>- | 0<br>- | 0<br>- | 1 (0.1)<br>- | 1 (<0.1)<br>- | 2 (<0.1)<br>- |
| Blood cancer (SCQ) | -<br>- | -<br>- | -<br>- | 2 (0.1)<br>0.1 | 2 (0.1)<br>- | 4 (0.1)<br>0.1 |
| B-cell lymphoma | 0<br>- | 0<br>- | 0<br>- | 1 (0.1)<br>- | 1 (<0.1)<br>- | 2 (<0.1)<br>- |
| Skin cancer (other than malignant melanoma) (SCQ) | -<br>- | -<br>- | -<br>- | 10 (0.7)<br>0.4 | 26 (1.1)<br>0.6 | 38 (0.9)<br>0.6 |
| Basal cell carcinoma | 1 (0.1)<br>0.3 | 5 (0.3)<br>0.9 | 2 (0.1)<br>0.5 | 7 (0.5)<br>0.3 | 17 (0.7)<br>0.4 | 24 (0.6)<br>0.3 |
| Squamous cell carcinoma of skin | 2 (0.2)<br>0.5 | 1 (0.1)<br>0.2 | 2 (0.1)<br>0.5 | 4 (0.3)<br>0.2 | 6 (0.3)<br>0.1 | 12 (0.3)<br>0.2 |
| Keratoacanthoma | 0<br>- | 1 (0.1)<br>0.2 | 0<br>- | 0<br>- | 4 (0.2)<br>0.1 | 4 (0.1)<br>0.1 |
| Solid cancer (including malignant melanoma) (SCQ) | -<br>- | -<br>- | -<br>- | 13 (0.9)<br>0.5 | 18 (0.8)<br>0.4 | 31 (0.8)<br>0.4 |
| Breast cancer | 0<br>- | 1 (0.1)<br>0.2 | 0<br>- | 1 (0.1)<br>- | 4 (0.2)<br>0.1 | 5 (0.1)<br>0.1 |
| Prostate cancer | 0<br>- | 1 (0.1)<br>0.2 | 1 (0.1)<br>0.2 | 2 (0.1)<br>0.1 | 3 (0.1)<br>0.1 | 5 (0.1)<br>0.1 |
| Thyroid neoplasm | 0<br>- | 0<br>- | 0<br>- | 1 (0.1)<br>- | 3 (0.1)<br>0.1 | 4 (0.1)<br>0.1 |
| Renal cell carcinoma | 0<br>- | 0<br>- | 0<br>- | 1 (0.1)<br>- | 2 (0.1)<br>- | 3 (0.1)<br>- |
| Metastases to lymph nodes | 0<br>- | 0<br>- | 0<br>- | 2 (0.1)<br>0.1 | 0<br>- | 2 (<0.1)<br>- |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period; -, Not calculated or <0.05

In the Japanese study PSOR-011, metastatic lung cancer and metastatic colon cancer, events classified as "malignant tumor (sponsor created query [SCQ])," were observed in 1 subject each in the 20 mg cohort, with the incidence of malignant tumor in the apremilast cohort being 0.8 per 100 subject-years.

In a large-scale global patient registry observational study PSOLAR involving 12,095 patients with psoriasis receiving systemic therapy (*J Drugs Dermatol.* 2014;13:1441-8), the incidence of malignant tumor (except non-melanoma skin cancer), adjusted for the observation period, was reported to be 0.58 per 100 subject-years in patients receiving infliximab (genetical recombination), 0.53 per 100 subject-years in patients receiving ustekinumab (genetical recombination), 0.74 per 100 subject-years in patients receiving other biological products, and 0.81 per 100 subject-years in patients receiving systemic therapy other than biological products. In a German patient registry study PsoBest involving 2444 patients with psoriasis receiving systemic therapy (*Arch Dermatol Res.* 2015;307:875-83), the incidence of malignant tumor (except non-melanoma skin cancer), adjusted for the observation period, was reported to be 0.46 per 100 subject-years in patients receiving systemic therapy other than biological products and 0.49 per 100 subject-years in patients receiving biological products. Among patients with psoriasis with plaque rash, the incidence of lymphohematopoietic malignancy was reported to be 0.262 per 100 subject-years (*Br J Dermatol.* 2009;160:1048-56), the incidence of non-melanoma skin cancer to be 0.31 to 1.53 per 100 subject-years (*J Invest Dermatol.* 2001;117:1531-7, *Br J Dermatol.* 2013;168:844-54, *Br J Dermatol.* 2012;166:1069-80), and the incidence of solid tumor including malignant melanoma to be 0.51 per 100 subject-years (*Br J Dermatol.* 2009;129:2604-12). As for patients with psoriatic arthritis, Clinical Practice Research Datalink (CPRD) estimates the incidence of hematopoietic malignancy to be 0.07 per 100 subject-years, the incidence of non-melanoma skin cancer to be 0.25 per 100 subject-years, and the incidence of solid tumor including malignant melanoma to be 0.54 per 100 subject-years.

Thus, no clear increase in the incidence of malignant tumor was observed in patients with psoriasis treated with apremilast compared with patients in the placebo group or patients treated with conventional anti-psoriatic drugs. Also, nonclinical studies of apremilast did not show any evidence of carcinogenicity. Based on these, the applicant considers that there is no evidence of risk of apremilast-induced malignant tumor, precluding the necessity of taking any particular measure currently.

PMDA has confirmed that the currently available data do not suggest the possibility of apremilast-induced increase in the risk of malignant tumor. However, the number of subjects evaluated in clinical studies and the period of evaluation are not sufficiently large to allow accurate evaluation of the risk of malignant tumor. Also, given the pharmacological action of apremilast, the possibility cannot be excluded that the mechanism of suppressing malignant tumor may be affected by apremilast. In addition, patients with psoriasis generally have a history of phototherapy and therapy with immunosuppressive drugs, raising concern about skin cancer in particular. Therefore, occurrences of malignant tumor should be continuously monitored in the post-marketing surveillance, etc.

### 7.R.3.5 Body weight decrease

The applicant's explanation on the incidences of body weight decrease during apremilast administration:
It is reported that PDE4B knock-out mice have decreased body weight, decreased white fat, etc. (*Endocrinology.* 2009;150:3076-82). Decreased body weight is observed also in clinical studies of roflumilast, a drug with PDE4-inhibitory activity. It is plausible that apremilast increases the intracellular cAMP level in adipose cells, which in turn affects lipid degradation, etc., resulting in body weight decrease, but the detailed mechanism is unknown.

Table 73 shows body weight changes in the apremilast pooled analysis. The change in body weight from baseline (mean ± SD) was −1.01 ± 3.21 kg in the 20 mg group, −1.21 ± 3.51 kg in the 30 mg group, and 0.11 ± 2.72 kg in the placebo group during the placebo-controlled period, and −0.95 ± 4.57 kg in the 20 mg cohort and −1.25 ± 6.11 kg in the 30 mg cohort during the apremilast administration period. The incidence of weight decreased (preferred terms [PT]) adjusted for the observation period was 2.1 per 100 subject-years in the 20 mg group, 3.2 per 100 subject-years in the 30 mg group, and 0.7 per 100 subject-years in the placebo group during the placebo-controlled period, and 0.8 per 100 subject-years (19 cases) in the 20 mg cohort and 1.0 per 100 subject-years (43 cases) in the 30 mg cohort during the apremilast administration period. No subjects experienced serious weight decreased (PT). Weight decrease leading to discontinuation of the study drug occurred in 2 subjects in the 20 mg cohort and 3 subjects in the 30 mg cohort during the apremilast administration period.

**Table 73. Change in body weight from baseline in apremilast pooled analysis**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects who had body weight measured | 900 | 1541 | 1274 | 1386 | 2281 | 3932 |
| Weight decrease by >20% | 1 (0.1) | 1 (0.1) | 1 (0.1) | 3 (0.2) | 17 (0.7) | 21 (0.5) |
| Weight decrease by >10% and ≤20% | 16 (1.8) | 22 (1.4) | 7 (0.5) | 69 (5.0) | 139 (6.1) | 211 (5.4) |
| Weight decrease by >5% and ≤10% | 84 (9.3) | 174 (11.3) | 36 (2.8) | 176 (12.7) | 320 (14.0) | 508 (12.9) |
| Weight decrease by ≤5% | 393 (43.7) | 729 (47.3) | 478 (37.5) | 516 (37.2) | 811 (35.6) | 1440 (36.6) |

Number of subjects (%)

Table 74 shows body weight changes in the Japanese study PSOR-011. The change in body weight from baseline (mean ± SD) was −0.56 ± 2.19 kg in the 20 mg group, −0.86 ± 1.81 kg in the 30 mg group, and −0.20 ± 2.37 kg in the placebo group during the placebo-controlled period, and −0.68 ± 2.81 kg in the 20 mg cohort and −1.08 ± 2.70 kg in the 30 mg cohort during the apremilast administration period. Weight decreased (PT) was observed in 1 subject in the 20 mg cohort.

**Table 74. Change in body weight from baseline in Japanese study PSOR-011**

| | Placebo-controlled period | | | Apremilast administration period | |
|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort |
| Number of subjects who had body weight measured | 85 | 85 | 84 | 121 | 120 |
| Weight decrease by >20% | 0 | 0 | 0 | 0 | 0 |
| Weight decrease by >10% and ≤20% | 1 (1.2) | 1 (1.2) | 1 (1.2) | 1 (0.8) | 1 (0.8) |
| Weight decrease by >5% and ≤10% | 4 (4.7) | 3 (3.5) | 3 (3.6) | 5 (4.1) | 7 (5.8) |
| Weight decrease by ≤5% | 39 (45.9) | 59 (69.4) | 31 (36.9) | 58 (47.9) | 78 (65.0) |

Number of subjects (%)

Table 75 shows the incidences of main adverse events in subjects with >5% decrease in body weight from baseline and in other subjects in PSOR Phase 3 pooled analysis. The incidences were generally similar between the two subject groups. Most of the gastrointestinal disorder-related events such as nausea and diarrhoea tended to occur and disappear within 4 weeks after the start of treatment [see "7.R.3.2 Gastrointestinal disorders"], while most of >5% decrease in body weight occurred ≥16 weeks after the start of treatment, showing no clear relationship between body weight decrease and gastrointestinal disorder.

Thus, a relationship between body weight decrease and apremilast is suggested from the greater number of subjects with body weight decrease in the apremilast group than in the placebo group. However, the applicant considers that body weight decrease is not a clinically significant change that would pose any particular problems, for the following reasons: (1) The body weight change from baseline is ≤5% in most of the subjects, and (2) there was no clear increase in the incidence of any adverse event in patients showing >5% decrease in body weight. Nevertheless, because the long-term effect of body weight decrease is unclear, the applicant will provide a caution statement in the package insert and continuously investigate the effect of body weight decrease in the post-marketing surveillance, etc.

**Table 75. Main adverse events in subjects with ≥5% decrease in body weight from baseline in PSOR Phase 3 pooled analysis**

| | Subjects with >5% decrease in body weight from baseline | Subjects without >5% decrease in body weight from baseline |
|---|---|---|
| | 30 mg cohort (n = 243, 520.2 subject-years) | 30 mg cohort (n = 941, 1418.9 subject-years) |
| All adverse events | 222 (91.4) [281.4] | 766 (81.4) [228.9] |
| Upper respiratory tract infection | 54 (22.2) [12.6] | 176 (18.7) [15.2] |
| Nasopharyngitis | 40 (16.5) [8.8] | 156 (16.6) [13.1] |
| Diarrhoea | 55 (22.6) [12.6] | 149 (15.8) [12.5] |
| Nausea | 46 (18.9) [10.8] | 149 (15.8) [12.4] |
| Tension headache | 23 (9.5) [4.9] | 92 (9.8) [7.3] |
| Headache | 21 (8.6) [4.3] | 64 (6.8) [4.7] |
| Vomiting | 22 (9.1) [4.5] | 41 (4.4) [3.0] |
| Decreased appetite | 11 (4.5) [2.2] | 21 (2.2) [1.5] |

Number of subjects (%); [ ], Incidence per 100 subject-years adjusted for total exposure period

PMDA's view:
The incidence of body weight decrease in the apremilast group tended to be higher than in the placebo group, warranting caution against body weight decrease in administering apremilast. Because of the limited number of subjects investigated currently, as proposed by the applicant, a caution statement on body weight decrease should be included in the package insert and, the occurrences of body weight decrease following treatment with apremilast and clinical effects associated with long-term body weight decrease should be investigated in the post-marketing surveillance, etc.

### 7.R.3.6 Cardiovascular-related events

The applicant's explanation on the incidences of apremilast-associated cardiovascular-related events:
The incidence of cardiovascular-related events in patients with psoriasis and in the general population is reported to be 1.64 and 1.16 per 100 subject-years, respectively (*Am J Med.* 2011;124:775.e1-6), suggesting a higher rate in patients with psoriasis than in the general population. It is reported that compounds with PDE4-inhibitory activity cause a catecholamine-stimulated increase in intracellular cAMP level in a human atrial preparation, eliciting arrhythmia (*Br J Pharmacol.* 2013;169:524-7). On the other hand, it is also reported that compounds with PDE4-inhibitory activity are not involved in the control of β1- or β2-receptor mediated inotropic or lusitropic action in the human heart (*Br J Pharmacol.* 2013;169:528-38). Thus, reports on the effect of PDE4 on the cardiovascular system are inconsistent.

Table 76 shows the incidences of cardiovascular-related events during the apremilast administration period in the apremilast pooled analysis.

**Table 76. Incidences of main cardiovascular-related events in apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Cardiac disorders (SOC) | 34 (3.4)<br>9.2 | 36 (2.2)<br>6.3 | 28 (2.0)<br>6.6 | 89 (6.1)<br>3.9 | 153 (6.5)<br>3.7 | 247 (6.0)<br>3.7 |
| Refined MACE (SCQ)[a)] | 1 (0.1)<br>0.3 | 2 (0.1)<br>0.3 | 3 (0.2)<br>0.7 | 11 (0.8)<br>0.5 | 18 (0.8)<br>0.4 | 29 (0.7)<br>0.4 |
| Acute myocardial infarction | 1 (0.1)<br>0.3 | 1 (0.1)<br>0.2 | 1 (0.1)<br>0.2 | 5 (0.3)<br>0.2 | 5 (0.2)<br>0.1 | 10 (0.2)<br>0.1 |
| Myocardial infarction | 0<br>- | 1 (0.1)<br>0.2 | 1 (0.1)<br>0.2 | 3 (0.2)<br>0.1 | 6 (0.3)<br>0.1 | 9 (0.2)<br>0.1 |
| Refined potential MACE (SCQ)[b)] | 5 (0.5)<br>1.3 | 5 (0.3)<br>0.9 | 5 (0.4)<br>1.2 | 26 (1.8)<br>1.1 | 38 (1.6)<br>0.9 | 65 (1.6)<br>0.9 |
| Angina pectoris | 2 (0.2)<br>0.5 | 1 (0.1)<br>0.2 | 3 (0.2)<br>0.7 | 9 (0.6)<br>0.4 | 20 (0.8)<br>0.5 | 29 (0.7)<br>0.4 |
| Angina unstable | 0<br>- | 0<br>- | 1 (0.1)<br>0.2 | 4 (0.3)<br>0.2 | 5 (0.2)<br>0.1 | 9 (0.2)<br>0.1 |
| Transient ischaemic attack | 1 (0.1)<br>0.3 | 1 (0.1)<br>0.2 | 0<br>- | 5 (0.3)<br>0.2 | 4 (0.2)<br>0.1 | 9 (0.2)<br>0.1 |
| Deep vein thrombosis | 0<br>- | 1 (0.1)<br>0.2 | 0<br>- | 2 (0.1)<br>0.1 | 4 (0.2)<br>0.1 | 7 (0.2)<br>0.1 |
| Myocardial ischaemia | 3 (0.3)<br>0.8 | 0<br>- | 1 (0.1)<br>0.2 | 5 (0.3)<br>0.2 | 1 (<0.1)<br>- | 6 (0.1)<br>0.1 |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period; -, Not calculated or <0.05

a) Defined by cardiac arrest, acute myocardial infarction, myocardial infarction, cerebrovascular accident, cerebral infarction, ischaemic stroke, brain stem stroke, stress cardiomyopathy, and haemorrhagic stroke.

b) Defined by peripheral arterial occlusive disease, angina unstable, transient ischaemic attack, angina pectoris, deep vein thrombosis, myocardial ischaemia, coronary artery occlusion, peripheral artery thrombosis, cerebral small vessel ischaemic disease, and femoral artery occlusion.

In the Japanese study PSOR-011, cardiovascular-related events observed were cerebral haemorrhage, coronary artery stenosis, and extrasystoles (1 subject each) in the 20 mg cohort and syncope (1 subject) in the placebo cohort.

The incidence of major adverse cardiac events (MACE) (death due to cardiovascular-related events, myocardial infarction, and cerebrovascular accident) adjusted for the observation period in patients with psoriasis was 0.36 per 100 subject-years (*J Drugs Dermatol.* 2014;13:1441-8), and the incidence of MACE (myocardial infarction, cardiac failure, death due to cardiovascular-related events, acute coronary syndrome, ischaemic stroke, cerebrovascular accident) in patients with psoriasis receiving systemic therapy with non-biological products and patients with psoriasis receiving biological products was 0.56 and 0.77 per 100 subject-years, respectively (*Arch Dermatol Res.* 2015;307:875-83). The incidence observed in clinical studies of apremilast was not higher compared with the incidence in the above reports.

In the clinical studies, most of the subjects with MACE or latent MACE had risk factors such as hypertension, hyperlipidemia, and obesity or co-morbid conditions such as coronary artery disease and atherosclerosis, precluding accurate evaluation of the relationship between apremilast and cardiovascular-related events. However, in light of the observations that (1) the incidence of cardiovascular-related events was similar between the apremilast group and the placebo group, that (2) the incidence of cardiovascular-related events did not show a tendency of increase with the duration of exposure to apremilast, and that (3) the incidence of cardiovascular-related events in the clinical studies of apremilast was not higher compared with the incidence in the population treated with conventional anti-psoriatic drugs, apremilast administration is unlikely to increase the risk of cardiovascular-related events.

PMDA confirmed that, currently, there is no evidence that suggests any apremilast-associated increase in the risk of cardiovascular-related events. However, since the number of subjects investigated in the clinical studies was not sufficiently large to allow accurate evaluation of the risk of cardiovascular-related events, close attention should be continuously paid to the possible effect of apremilast on the cardiovascular system in the post-marketing surveillance, etc.

### 7.R.3.7 Depression and suicide/self-injury

The applicant's explanation on the incidences of depression and suicide/self-injury during apremilast administration:

A 15-year cohort study involving 146,042 patients with mild psoriasis, 3956 patients with severe psoriasis for whom systemic therapy was indicated, and the general population consisting of 766,950 people without psoriasis showed that the incidence of depression-related events was 2.57, 3.18, and 1.70[38)] per 100 subject-years, respectively, and the incidence of suicide-related events was 0.093, 0.092, and 0.066[38)] per 100 subject-years, respectively, demonstrating a tendency of a higher incidence of depression- and suicide-related events in patients with psoriasis (*Arch Dermatol.* 2010;146:891-5). Nonclinical studies of apremilast did not detect any effect of apremilast on the central nervous system, precluding the identification of the mechanism of the occurrence of depression or suicide-related behaviors. However, since neuropsychiatric events such as depression are reported in patients treated with roflumilast, a drug with PDE4-inhibitory activity, the applicant investigated the occurrences of apremilast-associated depression and suicide-related events.

Table 77 shows the incidences of adverse events classified as "Depression (excl suicide and self-injury) (standardised MedDRA queries [SMQ])" or "Suicide/self-injury (SMQ)" in the apremilast pooled analysis.

**Table 77. Incidences of depression-related events and suicide-related events in apremilast pooled analysis (safety analysis population)**

| | Placebo-controlled period | | | Apremilast administration period | | |
|---|---|---|---|---|---|---|
| | 20 mg | 30 mg | Placebo | 20 mg cohort | 30 mg cohort | Apremilast cohort |
| Number of subjects | 999 | 1668 | 1411 | 1450 | 2357 | 4089 |
| Depression (excl. suicide and self-injury) (SMQ) | 12 (1.2)<br>3.2 | 19 (1.1)<br>3.3 | 8 (0.6)<br>1.9 | 53 (3.7)<br>2.3 | 73 (3.1)<br>1.7 | 129 (3.2)<br>1.9 |
| Depression | 10 (1.0)<br>2.7 | 17 (1.0)<br>3.0 | 8 (0.6)<br>1.9 | 47 (3.2)<br>2.0 | 63 (2.7)<br>1.5 | 111 (2.7)<br>1.6 |
| Depressed mood | 2 (0.2)<br>0.5 | 1 (0.1)<br>0.2 | 0<br>- | 6 (0.4)<br>0.2 | 8 (0.3)<br>0.2 | 15 (0.4)<br>0.2 |
| Suicide/self-injury (SMQ) | 2 (0.2)<br>0.5 | 2 (0.1)<br>0.3 | 1 (0.1)<br>0.2 | 3 (0.2)<br>0.1 | 3 (0.1)<br>0.1 | 6 (0.1)<br>0.1 |
| Suicidal ideation | 1 (0.1)<br>0.3 | 1 (0.1)<br>0.2 | 0<br>- | 2 (0.1)<br>0.1 | 1 (<0.1)<br>- | 3 (0.1)<br>- |
| Suicide attempt | 1 (0.1)<br>0.3 | 1 (0.1)<br>0.2 | 0<br>- | 1 (0.1)<br>- | 2 (0.1)<br>- | 3 (0.1)<br>- |
| Completed suicide | 0<br>- | 0<br>- | 1 (0.1)<br>0.2 | 0<br>- | 0<br>- | 0<br>- |

Upper row, number of subjects (%); Lower row, incidence per 100 subject-years adjusted for total exposure period
-, Not calculated or <0.05

In the Japanese clinical study PSOR-011, no adverse events classified as "Depression (excl. suicide and self-injury) (SMQ)" or "Suicide/self-injury (SMQ)" were observed throughout the entire administration period.

In the foreign post-marketing safety data, the incidence of adverse events related to "Suicide/self-injury (SMQ)" was 0.06% (65 of 104,754) of patients, showing no tendency of increase compared with the incidence in the clinical studies. Of 54 patients who showed non-fatal events, 48 patients discontinued apremilast, and of these, relapse of the symptoms was not observed after the discontinuation in 32 patients. Among the patients who had non-fatal events, 35 patients were evaluable for patient characteristics, and of these, 21 patients were found to have a past history of depression or factors for social stressors, whereas no suicide-related risk factors were detected in 14 patients, precluding the exclusion of a causal relationship of the non-fatal events to apremilast in all of them.

Results of the above cohort study reported that the incidence of depression and suicide-related events in patients with severe psoriasis for whom systemic therapy was indicated was 3.18 and 0.092 per 100 subject-years, respectively (*Arch Dermatol.* 2010;146:891-5). The incidence in the clinical studies of

[38)] The incidence of severe events

apremilast and in the foreign post-marketing safety data was not higher compared with the incidence in the cohort study.

Thus, the data so far available do not show that apremilast induces events related to depression, suicide, or self-injury. However, taking account of the fact that, in the foreign post-marketing safety data, there were patients with adverse events classified as "Suicide/self-injury (SMQ)" for which a causal relationship to apremilast could not be ruled out, the applicant will provide a caution statement in the package insert.

PMDA confirmed that the submitted clinical study data do not contain information that clearly indicates the relationship between apremilast and events related to depression or suicide/self-injury. However, since the foreign post-marketing safety data contain events for which a causal relationship with apremilast cannot be ruled out, occurrences of depression and suicide-related events should be continuously investigated in the post-marketing surveillance, etc.

Based on the above, PMDA considers that attention should be paid to infection, gastrointestinal disorders such as diarrhoea and nausea, headache, and body weight decrease during apremilast administration. However, all of these events were mild or moderate in severity and gastrointestinal disorder and headache were transient, apremilast is considered to be well tolerated. Nevertheless, it is necessary to closely monitor patients for possible occurrence of these events during apremilast administration and to take appropriate measure in the event of an occurrence. Studies in Japanese patients with psoriasis do not suggest any events requiring particular caution. However, because of the limited use experience currently, the safety profile of apremilast should be further clarified by collecting information from the post-marketing surveillance, etc.

### 7.R.4 Dosage and administration

The applicant's rationale for proposing the dose be gradually increased during the beginning of treatment and followed by 30 mg twice daily:
In the foreign phase I study in healthy adult subjects (Study CC-10004-PK-007), the incidence of adverse events related to gastrointestinal disorder tended to be lower in the apremilast 40 mg gradual dose increase group (once daily administration of 10 mg from Day 1 to Day 3, 20 mg from Day 4 to Day 6, 40 mg from Day 7 on) than in the apremilast 40 mg fixed dose group [see "7.1 Phase I study"]. Based on the results, the applicant considered it appropriate to start apremilast administration by gradual dose increase from 10 mg and, in the subsequent main clinical studies, the treatment was started by gradual dose increase.

In the foreign phase II study in patients with psoriasis vulgaris with plaque rash and patients with psoriatic arthritis with plaque rash (Study CC-10004-PSOR-003), the PASI 75 response rate in the 20 mg BID group was statistically significantly different compared with the placebo group, whereas the rate was comparable between the 20 mg QD group and the placebo group [see "7.2.1 Foreign phase II study"]. Therefore, in the Japanese bridging study (Study CC-10004-PSOR-011) and the foreign study to be bridged (Study CC-10004-PSOR-005), dose groups were select to allow comparison of dose response to apremilast, with the focus on 20 mg twice daily administration.

In the bridging study in patients with psoriasis vulgaris with plaque rash and patients with psoriatic arthritis with plaque rash (Study CC-10004-PSOR-011) and in the study to be bridged (Study CC-10004-PSOR-005), the PASI 75 response rate at Week 16 of administration, the primary endpoint, was statistically significantly different between the apremilast 20 mg group and the placebo group as well as between the apremilast 30 mg group and the placebo group. As shown in Table 78, apremilast 30 mg tended to be consistently more effective compared with apremilast 20 mg up to Week 52 of administration. Based on the results of the foreign phase II study (Study CC-10004-PSOR-005), the foreign phase III study in patients with psoriasis vulgaris with plaque rash and patients with psoriatic arthritis with plaque rash was conducted with apremilast 30 mg once daily administration. Results demonstrated the superiority of apremilast 30 mg to placebo in the PASI 75 response rate at Week 16 of administration, as shown in Table 79 [see "7.3.1 Foreign phase III study," "7.3.2 Foreign phase III study," and "7.3.3 Foreign phase III study"].

**Table 78. Changes in efficacy endpoint values over time in the bridging study and in the study to be bridged**

| | Dose | Week 16 | Week 32 | Week 52 |
|---|---|---|---|---|
| Bridging study (Study CC-10004-PSOR-011) | | | | |
| PASI 50 response rate | 20 mg | 37.6 (32/85) | 45.9 (39/85) | 57.6 (49/85) |
| | 30 mg | 48.2 (41/85) | 56.5 (48/85) | 64.7 (55/85) |
| PASI 75 response rate | 20 mg | 22.4 (19/85) | 25.9 (22/85) | 31.8 (27/85) |
| | 30 mg | 28.2 (24/85) | 35.3 (30/85) | 40.0 (34/85) |
| sPGA (0 or 1) response rate | 20 mg | 23.9 (17/71) | 32.4 (23/71) | 39.4 (28/71) |
| | 30 mg | 26.8 (19/71) | 33.8 (24/71) | 31.0 (22/71) |
| Study to be bridged (Study CC-10004-PSOR-005) | | | | |
| PASI 50 response rate | 20 mg | 44.8 (39/87) | 72.0 (36/50) | 48.0 (24/50) |
| | 30 mg | 56.8 (50/85) | 86.2 (50/58) | 72.4 (42/58) |
| PASI 75 response rate | 20 mg | 27.6 (24/87) | 38.0 (19/50) | 22.0 (11/50) |
| | 30 mg | 37.5 (33/88) | 46.6 (27/58) | 36.2 (21/58) |
| sPGA (0 or 1) response rate | 20 mg | 24.4 (21/86) | 26.0 (13/50) | 10.0 (5/50) |
| | 30 mg | 31.8 (28/88) | 44.8 (26/58) | 22.4 (13/58) |

% (number of subjects)

**Table 79. Efficacy in foreign clinical studies in patients with psoriasis with plaque rash**

| | Treatment group | Week 16 | Difference from placebo [95% CI] *P* value |
|---|---|---|---|
| Study CC-10004-PSOR-008 | | | |
| PASI 75 response rate | 30 mg | 33.1 (186/562) | 27.8 [23.1, 32.5] |
| | Placebo | 5.3 (15/282) | $P < 0.0001$[a)] |
| Study CC-10004-PSOR-009 | | | |
| PASI 75 response rate | 30 mg | 28.8 (79/274) | 23.0 [16.3, 29.6] |
| | Placebo | 5.8 (8/137) | $P < 0.0001$[a)] |
| Study CC-10004-PSOR-010 | | | |
| PASI 75 response rate | 30 mg | 39.8 (33/83) | 27.5 [14.9, 40.1] |
| | Placebo | 11.9 (10/84) | $P < 0.0001$[b)] |

% (number of subjects)
a) Chi-square test
b) Cochran-Mantel-Haenszel test stratified by BMI (≥30 and <30)

In the foreign phase II study in patients with psoriatic arthritis (Study CC-10004-PSA-001), apremilast 20 mg BID tended to be more effective than apremilast 40 mg QD [see "7.2.4 Foreign phase II study"], while there was no significant difference in safety between the 2 dosage regimen. In the foreign phase II study in patients with psoriasis vulgaris with plaque rash and patients with psoriatic arthritis with plaque rash (Study CC-10004-PSOR-005), a statistically significant difference was observed in the efficacy in the paired comparison between the apremilast 20 mg group and the placebo group and between the apremilast 30 mg group and the placebo group. Based on the above results, foreign phase III studies in patients with psoriatic arthritis were conducted by apremilast 20 and 30 mg twice daily administration. The foreign phase III studies in patients with psoriatic arthritis demonstrated the superiority of apremilast 20 and 30 mg to placebo in the ACR 20 response rate at Week 16 of administration, as shown in Table 80 [see "7.3.3 Foreign phase III study," "7.3.4 Foreign phase III study," "7.3.5 Foreign phase III study," and "7.3.6 Foreign phase III study"], and 30 mg tended to be consistently more effective than 20 mg up to Week 52.

**Table 80. Changes over time in efficacy endpoint values in the pooled analysis of clinical studies in patients with psoriatic arthritis (Studies CC-10004-PSA-002, 003, 004)**

| | Dose | Week 16 | Week 24 | Week 52 |
|---|---|---|---|---|
| ACR 20 response rate | 20 mg | 34.1 (160/469) | 43.9 (191/435) | 57.3 (204/356) |
| | 30 mg | 41.2 (185/449) | 45.8 (196/428) | 56.8 (212/373) |
| ACR 50 response rate | 20 mg | 15.1 (71/470) | 18.4 (80/435) | 25.6 (91/356) |
| | 30 mg | 15.5 (70/453) | 21.5 (93/432) | 24.6 (92/374) |
| ACR 70 response rate | 20 mg | 5.1 (24/473) | 6.2 (27/435) | 11.4 (41/360) |
| | 30 mg | 3.3 (15/457) | 7.6 (33/432) | 10.5 (39/373) |

% (number of subjects)

In these clinical studies, no safety problems of any special concern were observed in subjects in the apremilast 30 mg group [see "7.R.3 Safety"]. Therefore, the applicant considered it appropriate to select the dosage regimen as apremilast 30 mg twice daily both in patients with psoriasis vulgaris and in patients with psoriatic arthritis.

PMDA accepted the above explanation of the applicant and concluded it appropriate to select the dosage and administration of apremilast for patients with psoriasis vulgaris and for patients with psoriatic arthritis as proposed by the applicant.

### 7.R.5 Clinical positioning

#### 7.R.5.1 Positioning of apremilast relative to conventional anti-psoriatic drugs

The applicant's explanation on the clinical positioning of apremilast:

Patients with moderate to severe psoriasis are treated with systemic therapy using cyclosporine, etretinate, etc., or with phototherapy, and patients who have had an inadequate response to these therapies are treated with biological products. Enhanced production of cytokines such as IL-17, IL-23, and TNF-α is involved in the pathogenesis of psoriasis vulgaris and psoriatic arthritis (*Annu Rev Immunol.* 2014;32:227-55), and cyclosporine and biological products inhibit signal transduction mediated by these cytokines.

Tables 79, 80, and 81 show the efficacy of apremilast and biological products in the main clinical studies. As for the efficacy of cyclosporine, the PASI 75 response rate is reported to be 50% to 97% at doses of ≥5 mg/kg/day and 28% to 85% at doses of ≤2.5 mg/kg/day in a review of 428 literatures including randomized comparative studies (*J Eur Acad Dermatol Venereol.* 2011;25:19-27). As for the efficacy of etretinate, the PASI 50 response rate of 42% and PASI 70 response rate of 16% were reported at Week 12 of administration at doses of 0.5 to 0.75 mg/kg/day (*Am J Clin Dermatol.* 2001;2:41-7). Whereas the efficacy of apremilast for skin symptoms and joint symptoms in patients with psoriasis tended to be lower compared with high-dose (≥5 mg/kg/day) cyclosporine and biological products, apremilast did not show any tendency of lower efficacy compared with etretinate and cyclosporine (≤2.5 mg/kg/day), although caution is required in the interpretation of the results because of the comparison between different studies.

**Table 81. Efficacy of biological products**

| | Brodalumab (genetical recombination) | Ixekizumab (genetical recombination) | Secukinumab (genetical recombination) | Ustekinumab (genetical recombination) | Adalimumab (genetical recombination) | Infliximab (genetical recombination) |
|---|---|---|---|---|---|---|
| Proposed or approved dosage and administration | 210 mg s.c. at Week 0, 1, 2 and every 2 weeks thereafter | Initial dose of 160 mg s.c., followed by 80 mg s.c. every 2 weeks | 300 mg s.c. at Week 0, 1, 2, 3, 4, and every 4 weeks thereafter | 45 mg s.c. at Week 0, 4, and every 12 weeks thereafter | Initial dose of 80 mg s.c., followed by 40 mg s.c. every 2 weeks | 5 mg/kg i.v. infusion at Week 0, 2, 6, and every 8 weeks thereafter. The dose may be increased up to 6 mg/kg every 4 weeks or to 10 mg/kg every 8 weeks. |
| Efficacy in patients with psoriasis vulgaris | | | | | | |
| Study | Japanese study (4827-002) | Global study (RHAZ) | Global study (A2302) | Japanese study (JPN-02) | Japanese study (M04-688) | Japanese study (TA-650-15) |
| Evaluation time point | Week 12 | Week 12 | Week 12 | Week 12 | Week 16 | Week 10 |
| PASI 75 response rate | 94.6 (35/37) | 89.1 (386/433) | 81.6 (200/245) | 59.4 (38/64) | 62.8 (27/43) | 68.6 (24/35) |
| | Placebo: 25.6 (10/39) | Placebo: 3.9 (17/431) | Placebo: 4.5 (11/246) | Placebo: 6.5 (2/31) | Placebo: 4.3 (2/46) | Placebo: 0 (0/19) |
| Efficacy in patients with psoriatic arthritis (foreign studies only) | | | | | | |
| Study | Study 20101227 | RHAP study | Study F2312 | PSUMMIT 1 study | Study M02-518 | IMPACT study |
| Evaluation time point | Week 12 | Week 24 | Week 24 | Week 24 | Week 12 | Week 16 |
| ACR 20 response rate | 39.3 (22/56) | 62.1 (64/103) | 54.0 (54/100) | 42.4 (87/205) | 57.6 (87/151) | 65.4 (34/52) |
| | Placebo: 18.2 (10/55) | Placebo: 30.2 (32/106) | Placebo: 15.3 (15/98) | Placebo: 22.8 (47/206) | Placebo: 14.2 (23/162) | Placebo: 9.6 (5/52) |

% (number of subjects)

As for the safety, biological products pose safety concerns such as serious infection, opportunistic infection, and reactivation of latent tuberculosis infection, and are therefore positioned as drugs to be used in patients with inadequate response or intolerance to systemic therapy or phototherapy (*J Derm.* 2013;40:683-95). Use of etretinate requires caution against dyslipidemia and hyperostosis. In a Japanese clinical study, cyclosporine caused renal disorder-related adverse events and hypertension at high

incidences, including increased serum urea nitrogen in 40.2% (49 of 122) of subjects, hypertension in 29.5% (36 of 122) of subjects, and increased serum creatinine in 24.6% (30 of 122) of subjects (*J Dermatol.* 2003;30:290-8). Adverse events related to renal disorder and hypertension were also observed in the review of 428 literatures including randomized comparative studies (*J Eur Acad Dermatol Venereol.* 2011;25:19-27). Based on the above, it is recommended to preferably avoid long-term use of cyclosporine for ≥2 years and, during long-term use, to periodically monitor serum creatinine level (*The Japanese journal of dermatology*. 2004;114:1093-105).

In clinical studies in patients with moderate to severe psoriasis vulgaris or psoriatic arthritis, apremilast was shown to be effective for skin symptoms and joint symptoms. Taking account of these findings together with the safety profile of apremilast, convenience of administration, and usage conditions in foreign countries, it is considered appropriate to use apremilast as an oral preparation with a novel mechanism of action in patients with psoriasis who have had an inadequate response to topical therapy such as external treatment and require systemic therapy, in the treatment of moderate to severe psoriasis vulgaris and psoriatic arthritis.

Tables 82 and 83 show the results of a subpopulation analysis on patients with a history of systemic therapy other than biological products and patients with a history of treatment with biological products. Data were taken from foreign phase III clinical studies in patients with moderate to severe psoriasis vulgaris with plaque rash and patients with moderate to severe psoriatic arthritis with plaque rash (Studies CC-10004-PSOR-008 and CC-10004-PSOR-009) and from foreign phase III studies in patients with psoriatic arthritis (Studies CC-10004-PSA-002, CC-10004-PSA-003, and CC-10004-PSA-004). Apremilast improved the symptoms regardless of the presence or absence of a history of systemic therapy other than biological products or a history of treatment with biological products. Also, there were no differences in the incidences of adverse events between patients with a history of systemic therapy other than biological products or patients with or without a history of treatment with biological products. Based on the above, the applicant considers it appropriate to use apremilast regardless of a history of systemic therapy or use of biological products.

**Table 82. PASI 75 response rate at Week 16 of administration in patients with psoriasis with plaque rash, classified by prior treatment (pooled analysis of Studies CC-10004-PSOR-008 and 009, FAS, LOCF)**

| | Apremilast 30 mg | Placebo |
|---|---|---|
| The entire population | 31.7 (265/836) | 5.5 (23/419) |
| History of systemic therapy with ≥1 non-biological product | 27.8 (62/223) | 3.0 (3/101) |
| History of systemic therapy with ≥2 non-biological products | 18.9 (18/95) | 7.4 (4/54) |
| History of treatment with 1 biological product | 25.4 (43/169) | 5.2 (4/77) |
| History of treatment with ≥2 biological products | 24.7 (21/85) | 2.1 (1/47) |

% (number of patients)

**Table 83. ACR 20 response rate at Week 16 in patients with psoriatic arthritis, classified by prior treatment (pooled analysis of Studies CC-10004-PSA-002, 003, and 004, FAS, NRI)**

| | Apremilast 30 mg | Placebo |
|---|---|---|
| The entire population | 37.0 (184/497) | 18.8 (93/496) |
| Subjects with a history of treatment with biological products | 29.0 (31/107) | 8.9 (10/112) |
| Subjects who have had an inadequate response to biological products | 20.0 (7/35) | 5.1 (2/39) |

% (number of subjects)

PMDA's view:

Apremilast has been demonstrated to be effective for the treatment of patients with moderate to severe psoriasis vulgaris and psoriatic arthritis with plaque rash, and its safety profile does not have any particular clinical concern. Therefore, it is appropriate to consider that apremilast holds the same clinical positioning as conventional oral preparations used for systemic therapy, such as etretinate and cyclosporine, as one of the options for systemic therapy for moderate to severe psoriasis vulgaris and psoriatic arthritis with plaque rash that are inadequately responsive to topical therapies. Also, since apremilast has a novel mechanism of action different from that of conventional anti-psoriatic drugs, it is considered to be useful as a new treatment option for patients who cannot continue the treatment with etretinate and cyclosporine, a patient group also included in the clinical studies. However, since apremilast was found to be less effective than some biological products, albeit based on the comparison between different studies, apremilast is not recommended in patients requiring treatment with biological products, such as patients with severe psoriasis. Currently, there are no clinical data that directly

compared the efficacy between apremilast and etretinate or cyclosporine, precluding accurate comparison of the safety profile between apremilast and conventional anti-psoriatic drugs. Therefore, the clinical positioning of apremilast and choice between apremilast and conventional drugs should be investigated by relevant academic societies, etc., based on the results of post-marketing surveillance and appropriately conducted Japanese and foreign studies.

### 7.R.5.2 Concomitant use with conventional therapies

The applicant's explanation on the safety in the conceivable methods of concomitant use with apremilast, i.e., concomitant use with topical therapy with corticosteroid and active vitamin $D_3$, phototherapy, cyclosporine, and biological products:

In the foreign phase III studies (Studies CC-10004-PSOR-008 and CC-10004-PSOR-009) and in the Japanese phase II study (Study CC-10004-PSOR-011), subjects who became inadequately responsive to the study drug from Week 32 and 40, respectively, were allowed to receive either or both topical drugs and phototherapy. Table 84 shows the incidences of adverse events in subjects in these studies, classified by presence or absence of concomitant use with topical therapy or phototherapy. Although no clear conclusion could be reached because of the limited number of subjects investigated in these clinical studies, main events observed were diarrhoea, nausea, nasopharyngitis, and headache, and the incidence of adverse events did not show any significant difference depending on the presence or absence of concomitant use with topical therapy or phototherapy. Table 85 shows the safety profile in concomitant use of apremilast with topical therapy, cyclosporine, or biological products in the foreign post-marketing safety data. The safety was not significantly different from that observed in apremilast monotherapy.

**Table 84. Safety of apremilast in clinical studies, classified by concomitant therapy**

| | With concomitant topical therapy (n = 119) | Without concomitant topical therapy (n = 122) | With concomitant phototherapy (n = 11) | Without concomitant phototherapy (n = 230) |
|---|---|---|---|---|
| All adverse events | 72 (60.5) | 55 (45.1) | 4 (36.4) | 123 (53.5) |
| Diarrhoea | 4 (3.4) | 2 (1.6) | 0 | 6 (2.6) |
| Nausea | 3 (2.5) | 3 (2.5) | 1 (9.1) | 5 (2.2) |
| Headache | 4 (3.4) | 1 (0.8) | 0 | 5 (2.2) |
| Nasopharyngitis | 11 (9.2) | 7 (5.7) | 0 | 18 (7.8) |
| Upper respiratory tract infection | 10 (8.4) | 12 (9.8) | 2 (18.2) | 20 (8.7) |

Number of subjects (%)
From the safety data of Week 32 to 52 in Study CC-10004-PSOR-008

**Table 85. Safety based on the foreign post-marketing safety data, classified by concomitant drugs**

| | Apremilast monotherapy population (n = 30,373) | Apremilast + cyclosporine population (n = 111) | Apremilast + biological product population (n = 981) | Apremilast + corticosteroid population (n = 935) | Apremilast + topical vitamin $D_3$ population (n = 1341) |
|---|---|---|---|---|---|
| Gastrointestinal disorders (SOC) | 10,562 (34.8) | 37 (33.3) | 314 (32.0) | 337 (36.0) | 451 (33.6) |
| Diarrhoea | 3460 (11.4) | 8 (7.2) | 101 (10.3) | 122 (13.0) | 131 (9.8) |
| Nausea | 3297 (10.9) | 18 (16.2) | 83 (8.4) | 99 (10.6) | 129 (9.6) |
| Infections and infestations (SOC) | 1207 (4.0) | 1 (0.9) | 36 (3.7) | 36 (3.9) | 56 (4.2) |
| Psychiatric disorders (SOC) | 1926 (6.3) | 5 (4.5) | 63 (6.4) | 55 (5.9) | 74 (5.5) |
| Cardiac disorders (SOC) | 206 (0.7) | 0 | 10 (1.0) | 6 (0.6) | 10 (0.7) |

Number of affected patients (%)

PMDA's view:

Although no particular problems were suggested in the cases of combination therapy, it is practically impossible currently to draw any conclusion on the safety of concomitant use of apremilast with conventional anti-psoriatic drugs because of insufficient data available. Given that apremilast has a pharmacological effect that may affect immune function and that cyclosporine and biological products have a potential risk of causing serious infection, the possibility cannot be excluded that concomitant use of apremilast with these conventional drugs might enhance the risk. Thus, patients should be closely monitored in concomitant use apremilast with conventional anti-psoriatic drugs. Also, information on

the concomitant use with systemic therapy, phototherapy, and topical therapy should be collected in the post-marketing surveillance to carefully evaluate the safety and efficacy in such regimens, and the information thus obtained should be provided to healthcare professionals.

### 7.R.6 Indications

Based on the review of the submitted data and on the review as described in "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.5 Clinical positioning," PMDA concluded as follows:
It is appropriate to indicate apremilast for psoriasis vulgaris and psoriatic arthritis. However, taking account of the patients investigated in the clinical studies and of the clinical positioning of apremilast, apremilast should be indicated for patients with psoriasis vulgaris with skin rash covering ≥10% of the body surface area for which topical therapy is considered unsuitable or that is inadequately responsive to topical therapy, requiring systemic therapy or phototherapy, and for patients with psoriatic arthritis.

The above conclusion by the PMDA will be finalized based on the review at the Expert Discussion.

### 7.R.7 Post-marketing safety measures

The applicant's explanation on post-marketing safety measures:
It is critical to start apremilast by gradual dose increase in order to decrease the incidence of gastrointestinal disorders such as diarrhoea. To facilitate the compliance with the appropriate method for apremilast administration, the applicant will prepare product sheet sets (starter packs), each containing tablets for the first 14 days in accordance with the gradual dose increase schedule up to Day 6. Each set of the product sheets will be supplied together with an instruction leaflet containing descriptions of the method for administration, precautions for administration, adverse events likely to occur during the early stage of treatment and countermeasures, actions to be taken in case of administration error, to promote awareness.

The applicant also will prepare information materials for healthcare professionals for the proper use of apremilast, including the descriptions for facilitating the administration by gradual dose increase at the start of the treatment, information on the safety of apremilast, precautions for use, etc.

In addition, the applicant will conduct a post-marketing surveillance to investigate the safety, efficacy, etc., in routine clinical use and, based on the data obtained from the post-marketing surveillance and on the safety information in foreign countries, the applicant will provide newly obtained safety information and other information on apremilast to healthcare professionals as necessary and, at the same time, provide information on the incidences of adverse drug reactions after the market launch on the home page of the applicant.

PMDA's view on the post-marketing safety measures:
Currently, the review in "7.R.3 Safety" does not suggest any serious safety concern in apremilast. However, caution should be paid to gastrointestinal disorder such as diarrhoea and nausea, infection, headache, and decreased body weight in administering apremilast, although no serious safety concern has been raised. Since apremilast has pharmacological activity to suppress the production of various cytokines, due caution should be exercised against infection. It is desirable that patients to be treated with apremilast be appropriately diagnosed and selected, that apremilast be used by physicians who are well experienced in the diagnosis and treatment of psoriasis and have a thorough knowledge of the profile of apremilast so that apremilast is used appropriately, and that, in case of adverse drug reactions, apremilast be used in a medical institution where cooperation with other departments/facilities is available. In addition, the applicant should prepare information materials for healthcare professionals to promote compliance with apremilast administration and provide safety information, thereby facilitating proper use.

A post-marketing surveillance should be conducted in order to identify the safety profile of apremilast, including the occurrences of unknown adverse events. At the same time, information on the occurrences of neuropsychiatric events, serious infection, malignant tumor, cardiovascular events, etc., during the long-term treatment should be collected. Additional safety information obtained after the market launch should be provided appropriately and promptly to healthcare professionals and to patients.

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

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

The new drug application data were subjected to a document-based compliance inspection and data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application (CTD5.3.5.1.6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. The following finding was noted in the sponsor's work, although it did not significantly affect the evaluation of the study as a whole. These were notified to the applicant (sponsor) for improvement.

**Matters that should be improved**

Sponsor

- Delay in the periodical report on safety information to the investigator and the head of the clinical trial site.

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

PMDA has concluded that the submitted data demonstrated the efficacy of Otezla in the treatment of patients with psoriasis vulgaris and psoriatic arthritis and acceptable in view of the benefits indicated by the data submitted. Otezla is an anti-psoriatic drug with a new mechanism of action, providing a new treatment option for psoriasis, and thus has a clinical significance. Data of clinical studies, etc., do not pose any particular safety problem. However, the safety of apremilast should be further evaluated in routine clinical use in the post-marketing surveillance.

PMDA has concluded that Otezla may be approved if Otezla is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

November 14, 2016

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Otezla Tablets 10 mg<br>Otezla Tablets 20 mg<br>Otezla Tablets 30 mg |
| **Non-proprietary Name** | Apremilast |
| **Applicant** | Celgene K.K. |
| **Date of Application** | March 24, 2016 |

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

### 1.1 Efficacy, safety, indications, and dosage and administration

The following comments were raised from the expert advisors at the Expert Discussion. The PMDA's conclusion on the efficacy, safety, indications, and dosage and administration of Otezla Tablets 10 mg, 20 mg, and 30 mg described in the Review Report (1) was supported by the expert advisors.

- As with the conventional oral medications for systemic therapy such as etretinate and cyclosporine, apremilast is expected to be recognized in clinical practice as an option for systemic therapy. However, because of strongly suggested apremilast's lower efficacy than conventional biological products, biological products should preferentially be used to treat severely affected patients.

- A joint lesion of psoriatic arthritis may lead to irreversible change. Apremilast treatment should not be continued carelessly in patients with psoriatic arthritis who have had an inadequate response to the treatment.

- Unlike the conventional oral medications for psoriasis, the dose of apremilast is gradually increased at the beginning of treatment. Healthcare professionals and patients must be fully informed of the initial gradual dose increase in the regimen.

- It is a fact that there are no clinical data recommending the use of apremilast 30 mg once daily in patients with severe renal impairment. However, preferably, healthcare professionals should be provided with dose selection guidelines for these patients.

Taking account of the above comments from the expert advisors, PMDA gave the applicant the following instructions, to which the applicant responded appropriately.

- In order to avoid apremilast treatment being continued carelessly in patients who have had an inadequate response to the treatment, the package insert, etc. should stress the importance of careful judgment on whether to continue the treatment based on the effect of apremilast treatment.

- The package insert should stress the importance of adherence to the regimen with initial gradual dose increase, with the fact that nausea, diarrhea, vomiting, etc. occurred more frequently in patients who had not undergone initial gradual dose increase than in those who had undergone, in the "Precautions for Dosage and Administration" section.

- The package insert should provide the guideline for the dosage regimen (30 mg once daily) of apremilast for patients with severe renal impairment based on the results of the population

pharmacokinetic analysis. Physicians should be advised to carefully administer apremilast to these patients.

### 1.2 Risk management plan (draft)

In view of the discussion in Section "7.R.7 Post-marketing safety measures" of the Review Report (1), PMDA has concluded that the risk management plan (draft) for apremilast should include the safety and efficacy specifications presented in Table 86, and the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 87.

**Table 86. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Serious hypersensitivity<br>• Serious infection<br>• Gastrointestinal disorder | • Vasculitis<br>• Depression- and suicide-related events<br>• Malignant tumor<br>• Decreased body weight | • None |
| Efficacy specification | | |
| • Efficacy in patients with psoriasis vulgaris and patients with psoriatic arthritis in routine clinical use | | |

**Table 87. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance<br>• Use-results survey (psoriasis vulgaris and psoriatic arthritis) | • Early post-marketing phase vigilance<br>• Preparation of materials for healthcare professionals (guidelines for proper use) |

PMDA instructed the applicant to conduct post-marketing surveillance to investigate these items.

The applicant's explanation about its plan for use results survey:
Table 88 is a summary of a use-results survey to be conducted in patients with psoriasis vulgaris who have had an inadequate response to topical therapy and patients with psoriatic arthritis. The target sample size is 1000 patients and the observation period 12 months. The survey will be aimed to investigate the safety and efficacy of apremilast in routine clinical use, with key survey items, namely serious infection, gastrointestinal disorder, serious hypersensitivity, vasculitis, depression and suicide-related events, malignant tumor, and decreased body weight, and to investigate the safety and efficacy in patients with renal impairment.

**Table 88. Outline of use-results survey (psoriasis vulgaris and psoriatic arthritis) (draft)**

| | |
|---|---|
| Objective | To investigate the safety and efficacy in routine use of apremilast |
| Survey method | Central registration |
| Population | Patients with psoriasis vulgaris who have had an inadequate response to topical therapy and patients with psoriatic arthritis |
| Observation period | 12 months |
| Planned sample size | 1000 |
| Main survey items | • Key survey items: Serious infection, gastrointestinal disorder, serious hypersensitivity, vasculitis, depression and suicide-related events, malignant tumor, and decreased body weight<br>• Patient characteristics (e.g., body weight, age, type of psoriasis, severity, disease duration, prior treatment, comorbidities)<br>• Apremilast treatment status<br>• Concomitant drugs/therapies<br>• Laboratory tests<br>• Adverse events<br>• Efficacy |

## 2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration modified as below, with the following condition. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as a powerful drug.

**Indications**

Psoriasis vulgaris~~that is deemed inappropriate for topical therapy or that has been insufficiently responsive~~ inadequately responding to topical therapy
Psoriatic arthritis

(Underline denotes additions, and strikethrough denotes deletions.)

**Dosage and Administration**

The usual adult oral dose of Apremilast is ~~gradually increased according to the schedule~~ shown below. From Day 6 onward, Apremilast is administered orally twice daily in the morning and evening at a dose of 30 mg.

~~Schedule for gradual dose increase~~

| | Morning | Evening |
|---|---|---|
| Day 1 | 10 mg | - |
| Day 2 | 10 mg | 10 mg |
| Day 3 | 10 mg | 20 mg |
| Day 4 | 20 mg | 20 mg |
| Day 5 | 20 mg | 30 mg |
| Day 6 and thereafter | 30 mg | 30 mg |

(Underline denotes additions, and strikethrough denotes deletions.)

**Condition of Approval**

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